Factors associated with the uptake of HIV testing and treatment in the first year of the HPTN 071 (PopART) intervention.

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Statement of own work

I, Kalpana Sabapathy, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Introduction

The HPTN 071 (PopART) trial is a community randomised trial in Zambia and South Africa, examining the impact of combination prevention, including treatment as prevention using Universal Test and Treat (UTT), on community level HIV-incidence. This PhD evaluates the factors associated with uptake of the key interventions, during the first year of the trial.

Methods

Two systematic reviews were conducted on home-based HIV testing and counselling (HB-HTC), and the cascade-of-care following community-based HTC, respectively. In addition, two case-control (CC) studies were nested within PopART, to examine factors associated with the uptake of the door-to-door home-based universal testing (CC study 1), and universal treatment (CC study 2) interventions.

Results

Our results suggest that HB-HTC in sub-Saharan Africa is widely accepted – uptake among those offered HB-HTC was 83% in a systematic review and meta-analysis of studies (2000-2012). The second systematic review found considerable variability in measures used to report linkage-to-care and ART initiation and in outcomes reported, even for similar time periods following HIV-detection (studies between 2006-2016).

CC1 found no differences between acceptors and non-acceptors of HB-HTC by demographic and behavioural characteristics. CC2 identified that the more lifetime sexual partners participants reported, the more likely they were to achieve timely linkage and ART initiation (TLA). Negative perceptions about clinic infra-structure were associated with failure to achieve TLA.

Both CC studies found that favourable views about the Community HIV-care Providers was associated with uptake of interventions, while neither stigma nor unfavourable views about clinic staff were associated with uptake.

Conclusion

This PhD contributes to knowledge on the cascade-of-care and UTT. It suggests that PopART interventions are acceptable across population sub-groups, providing optimism for achieving universal coverage using the PopART model to implement UTT. If individuals with high-risk sexual behaviour embrace interventions as we observed, there is great promise for treatment as prevention.

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Contents

List of abbreviations

ART	**Antiretroviral treatment**
CC	**Case-control**
CC1	**Case-control Study 1**
CC2	**Case-control Study 2**
CHiP	**Community HIV-care Provider**
EDC	**Electronic Data Capture**
HB-HTC	**Home-based HIV Testing and Counselling**
HCW	**Health Care Worker**
HCF	**Health Care Facility**
HPTN	**HIV Prevention Trials Network**
HTS	**HIV Testing Service(s)**
LTC	**Linkage-to-care**
PAF	**Population Attributable Fraction**
PLWH	**People Living With HIV**
PMTCT	**Prevention of Mother To Child Transmission**
RA	**Research Assistant**
RNA	**Ribonucleic Acid**
SSA	**Sub-Saharan Africa**
TLA	**Timely Linkage-to-ART**
TB	**Tuberculosis**
UTT	**Universal Test and Treat**
VMMC	**Voluntary Medical Male Circumcision**
WHO	**World Health Organization**

Chapter 1: Introduction

Outline of Chapter

This chapter describes the structure of the thesis and introduces the background to the PhD. It summarises the HIV epidemic in sub-Saharan Africa, and explains Treatment as Prevention and the concept of Universal Test and Treat (UTT). It also describes in summary the design of the HPTN 071 (PopART) trial within which the PhD primary research is nested and goes on to outline the rationale of the components of the PhD.

1.1 Structure of the PhD thesis

The purpose of this PhD is to evaluate the factors associated with uptake of the key steps in the cascade of care in the UTT model provided by the PopART trial. To that end, two nested case-control (CC) studies were done to examine the factors associated with the uptake of the door-to-door home-based universal testing (CC study 1), and universal treatment (CC study 2) interventions. In order to inform and place the respective studies in context, two systematic reviews were conducted on HB-HTC and the cascade of care following community-based HIV detection, respectively.

This first chapter lays out the context of research done for the PhD as described above. In chapter 2 of this "paper-style" PhD thesis document, the methods of the primary research conducted are described in greater detail than could be presented in the manuscripts of the studies which were submitted for publication. In chapter 3, the published manuscript of the systematic review on HB-HTC which helped inform the first case-control study is presented. Chapter 4 presents the manuscript which has been submitted for publication on CC study 1 which examines the factors associated with uptake of HB-HTC during the first year of the PopART intervention. The manuscript of the second systematic review which was undertaken to examine the cascade of care following HTC done in the community is presented in chapter 5. Chapter 6 presents the second case-control study on the factors associated with timely linkage to ART during the first year of PopART. Finally, Chapter 7 discusses the findings of the PhD, examines the strengths and limitations and reflects on the potential implications of the research conducted.

1.2.1 HIV epidemic in sub-Saharan Africa

Great progress has been made globally in the response to the HIV epidemic in recent years, not least in the Eastern and Southern African region. (1) With an estimated 10.3 million people on antiretroviral treatment (ART) in the region, this represents 54% of the 19 million people living with HIV on ART – more than twice what coverage was in 2010. This has helped reduce the number of deaths due to HIV to 470,000 in 2015 from 760,000 in 2010. The result is an increase in the number of people living with HIV. Despite the positive developments there are other more sobering data to consider. HIV incidence has remained essentially static at 2.1 million per year globally and has

reduced by just 4% since 2010 to just below 1 million new infections in 2015 in the Eastern and Southern Africa region.

The importance of preventing new infections is obvious at the individual level. At a public-health level HIV prevention helps reduce the burden on struggling health systems especially across sub-Saharan Africa - in terms of reduction in HIV related co-morbidities and the cost of long-term ART provision for what would otherwise be ever increasing numbers of people living with HIV. There is a global commitment to end the AIDS epidemic by 2030 and UNAIDS recommends a Fast-Track approach which involves front-loading investment over the next five years "to overcome within 15 years one of the greatest public health challenges in this generation". (1) There is therefore an urgent need to deliver on HIV prevention goals. It is acknowledged that a combination of prevention methods is needed in order to achieve steep reductions in HIV incidence (2-4).

1.2.2 Treatment as prevention

HIV-infected individuals require ART to remain healthy in the longer term. The optimal timing of ART initiation has been a subject of on-going research and convincing evidence now exists for the benefits of early initiation.(5, 6) The TEMPRANO trial showed a reduction by 44% of serious illness and death when ART was initiated at a CD4-count >500/cc3 and the START trial observed a 57% reduction in death, AIDS and serious non-AIDS events in those in the intervention arm which received immediate ART (median CD4-count of 651/cc3) vs those randomised to ART at CD4-count <350/cc3. The evidence in favour of starting treatment earlier for the HIV-infected individual's own health has meant that the latest World Health Organization (WHO) guidelines now recommend initiation of ART for all those living with HIV irrespective of CD4-count.(7)

The achievements in prevention of transmission from mother to child (PMTCT) have provided the proof needed that treatment can be used to prevent transmission and have led to the prospect of elimination of infant HIV-infection. (8-11) The biological rationale for using treatment to prevent sexual transmission was provided by observational data in studies which showed that when HIV-infected individuals had plasma viral loads of <400 HIV RNA copies/ml, no transmission to sexual partners occurred (12-14).

"Treatment as prevention", the concept of using treatment for HIV-infected individuals to achieve viral suppression so that the risk of transmission to uninfected sexual partners is negligible, therefore arose. The HIV Prevention Trials Network (HPTN) 052 randomised controlled trial, which examined this concept within clinical trial settings, showed at final analysis a 93% reduction in linked HIV transmissions from HIV-infected to uninfected partners when the former were treated early (ART initiated between CD4 counts >350 cells/mm3 and <550 cells/mm3) compared to late (CD4

counts <250 cells/mm3).(15) There were 3 linked transmission events in the early treatment arm compared to 43 in the late treatment arm, and there were no linked transmission events observed if the HIV-positive partner was stably suppressed on ART. Similarly, results from the PARTNER Study found no evidence of linked transmission between couples — a zero rate of HIV transmission if the HIV-positive partner had a suppressed viral load (< 200 copies/ml) on ART.(16)

Mathematical modelling studies have also suggested that dramatic reductions in the incidence of HIV at a population level can be achieved using antiretroviral treatment as prevention. (17-19) While conclusions of some of these studies have been questioned (20), the interest in exploring the treatment as prevention strategy at scale has not diminished (7, 21).

A large population-based prospective cohort of HIV uninfected individuals in South Africa provided ecological evidence that the risk of HIV acquisition is inversely proportional to local ART coverage.(22) Nonetheless, research on the public health benefit of using treatment as prevention remains an urgent priority, not least to determine the feasibility of delivery at large scale.

1.2.3 Universal test and treat

'Universal test and treat' (UTT) aims to maximize the effects of treatment as prevention by delivering universal voluntary HIV testing throughout the community, with effective linkage-to-care for immediate offer of ART irrespective of immune-status.(23) The universal testing component which actively provides HIV-testing to increase knowledge of HIV status at a large scale, combined with active referral for timely care and treatment means that UTT goes beyond just "immediate treatment" for those presenting for HIV care.

The community-wide identification of HIV-infected individuals is regarded as one of the corner-stones of effective early treatment and is a pre-requisite for successful treatment as prevention at a public-health level.(24, 25) Following diagnosis, HIV-infected individuals require timely linkage-to-care for clinical assessment with minimal delay. Under existing treatment guidelines in many countries which have not yet adapted to changes in WHO guidelines of treatment for all HIV-infected, upon successful linkage, maintenance in "pre-ART" care is generally required. "Pre-ART" care is for those who are not yet eligible for ART, until ART initiation criteria are met and treatment can be commenced.(26) As any HIV-infected individual who links into care will be immediately eligible for ART within a UTT approach, the "pre-ART" care step is effectively removed, or minimised to a very short period of time (only to allow for the preparatory processes for ART initiation which may include CD4 count, liver and kidney function testing for clinical evaluation purposes, ART preparedness counselling etc).

Emerging evidence suggests that once those living with HIV reach care, acceptability of ART initiation at any CD4-count is high. (27, 28) The challenge seems to lie in linkage-to-care.(27, 28) In the context of UTT individuals must successfully achieve timely linkage-to-ART (TLA) in order for optimal benefit of "immediate ART". Most individuals in a UTT context will be diagnosed in community settings, and linkage to care requires reaching the clinic and registering for care, in contrast with health facility diagnosed patients who are usually already at the location where HIV care will be provided, thus making registration for care much easier. Successful TLA requires individuals who may be asymptomatic and who had not considered themselves at risk of HIV to link-to-care without delay, as well as initiate ART as soon as possible. The latter requires efficient functioning of health-systems as well as willingness on the part of people living with HIV (PLWH).

Ending the AIDS epidemic, defined as a reduction of HIV incidence to ~200,000 by 2030, so that HIV is no longer a major public health threat is a goal which has been set by UNAIDS with global consensus. It has been stated that "it will be impossible to end the epidemic without bringing HIV treatment to all who need it".(29) With this ambitious goal in sight, the 90-90-90 targets were released in 2014. The targets are that by 2020 - 90% of all people living with HIV will know their HIV status; 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and; 90% of all people receiving antiretroviral therapy will have viral suppression. In combination, achieving these three targets would lead to 73% of PLWH being virally suppressed, and mathematical models suggest this would enable the ending of the AIDS epidemic by 2030.(29)

While these targets provide much needed motivation to improve, current realities in most of sub-Saharan Africa are not quite achieving them. Lack of services and /or services which are inaccessible or too inconvenient for users (in relation to competing priorities of daily life) have been identified as key failings in the cascade.(30-32) Lack of awareness about the benefits of knowledge of HIV status and early linkage-to-care, especially in individuals who are asymptomatic has been found to be another major gap.(31, 33, 34) The on-going requirement in many settings to meet eligibility criteria before starting ART is also an obstacle.(34, 35) Negative perceptions of PLWH, of HIV services and of ART have been shown to act as further barriers in the cascade. (30, 36)

1.2.4 Treatment as prevention community randomised trials[1]

The ANRS 12249 TasP trial team announced sobering results from their trial in rural South Africa, of the impact of UTT on HIV-incidence. They found no reduction in HIV-incidence when comparing a

[1] The designs of the trials described here are as they were originally planned. Following the change in WHO guidelines in 2015 to offer ART to all HIV-positive individuals, all the trials changed practice accordingly, including in control arms which previously offered ART according to CD4-count criteria recommended in national guidelines.

UTT arm with 6 monthly HB-HTC and referral for care at trial clinics which provided immediate ART vs an arm with 6 monthly HB-HTC and referral for care at trial clinics which provided ART according to national guidelines (initially <350/cc3, transitioning to <500/cc3). (37) While they observed high acceptability of HB-HTC and high proportions with viral suppression on ART at 3 months (in both study arms), linkage-to-care proved to be the weak link in the cascade. Rather than the desired 90-90-90 target, what was achieved was 92-49-93 in the intervention arm and 93-46-94 in the control arm, resulting in no difference in HIV incidence between the study arms. In addition, rather than the target 73% of PLWH virally suppressed, 43% were virally suppressed in the UTT arm. These results provide important lessons for other UTT initiatives although at this stage we must be cautious when generalising beyond the rural South African setting of the trial. The TasP trial was also only examining the impact of immediate treatment vs treatment with eligibility criteria. Other UTT trials are examining other aspects of the treatment cascade such as the added benefit of universal testing vs current standards of HIV test provision, or emphasis on patient-centred services to enhance linkage-to-care – in addition to the impact of immediate treatment.

The SEARCH study has reported much more optimistic interim results from process data of the initial phase of their community randomised trial in Uganda and Kenya.(38) This study is delivering a multi-disease community based campaign combined with a streamlined service delivery model designed to reduce structural barriers, improve patient-clinician relationships, and enhance patient knowledge and attitudes about HIV. After two years of implementation, the SEARCH team report that 81% of PLWH were virally suppressed having exceeded UNAIDS targets by achieving 97-93-90 at each of the key steps.

The Botswana Combination Prevention Project (BCPP) is another UTT trial which is exploring the impact of combination prevention including home-based and mobile HIV testing and counselling; point-of-care CD4 testing; linkage to care support; expanded ART (for CD4 351–500 cells/mm3 or CD4 >500 with HIV-1 RNA≥10,000 copies/mL, in addition to local criteria); and enhanced male circumcision services, on HIV incidence at a population level. (39) Results from a baseline population survey indicate that 70% of PLWH were virally suppressed (83-87-97 for each of the target steps).

The HPTN 071 (PopART) trial (Population Impact of Antiretroviral Treatment to Reduce Transmission) is the largest HIV prevention trial to date. (40) It is examining the impact of delivering UTT in Zambia and South Africa. Results have been published after one year of implementing the full trial intervention of door-to-door testing and treatment for all PLWH in Zambia, on the first two UNAIDS targets. (27) These indicate that among PLWH an estimated 78% of men and 87% of women were aware of their HIV positive status and approximately three-quarters of them were on ART after

one year. The primary research of this PhD is nested within PopART and it is therefore described in greater detail below.

1.3 Summary of HPTN 071 (PopART) Trial

The HPTN 071 (PopART) trial is a 3-arm community randomised trial which is testing the hypothesis that a combination prevention package including UTT can substantially reduce HIV incidence at a population level.(40) PopART is being conducted in 21 communities in Zambia and South Africa and commenced in November 2013 (see Figure 1.1 and Appendix 1). The trial applies a combination prevention approach which combines UTT with other proven HIV prevention methods. This includes wide-scale promotion of voluntary medical male circumcision (VMMC), which has been shown to reduce acquisition of HIV-infection in men by 60% in trials in sub-Saharan Africa (SSA) (41-43), as well as prevention of mother-to-child transmission (PMCT), and behavioural elements including condom promotion.

The 21 trial communities were grouped into seven matched triplets (four in Zambia and three in South Africa) based on geographical proximity, implementing partners for HIV services and estimated adult HIV prevalence. Allocation of the communities into three study arms was carried out using a process of restricted randomisation to ensure overall balance across study arms on cluster size, ART uptake at baseline and HIV prevalence.

Seven communities (four in Zambia and three in South Africa) in the main intervention arm (Arm A) have been receiving the full PopART package described above from the start of the trial. Seven Arm B communities were receiving the same package but with ART eligibility according to national guidelines (these changed from CD4 counts of <350 to <500/mm3). These two intervention arm communities were designed to be compared with the standard of care arm (Arm C) communities which were receiving not only ART according to national guidelines, but also testing and linkage-to-care as was standard at the time. The trial schema shown in Figure 1.1 summarises the intervention arms based on the original design of the trial.

Following the change to WHO guidelines in 2015 all PopART communities, including those in Arms B and C, have switched to ART eligibility for all PLWH, in keeping with best practice and ethical principles. Arms A and B are therefore now receiving the same package, while Arm C remains different in terms of testing, linkage-to-care and promotion of other prevention services. Mathematical modelling suggests that the impact of intervening on HIV testing and linkage-to-care is likely to see a significant impact on HIV-incidence, over and above the impact of switching to ART eligibility for all without increasing knowledge of HIV status and/or enhancing linkage-to-care of those tested HIV-positive. (19)

The cornerstone of the PopART intervention is the service provide by the Community HIV-care Providers (CHiPs) which is summarised in Figure 1.2. This cadre of staff are members of the community who were hired and trained by PopART to work in their communities to provide the services available to the intervention communities. In summary, a team of CHiPs are responsible for delivering services to a zone within a community of approximately 500 households. Each team ideally consists of a man and a woman who speak the prevalent local languages. CHiPs use handheld electronic devices to record intervention data which in turn are used to aid service delivery e.g. for following-up PLWH who have been referred for HIV care etc.

The CHiPs attempt to conduct annual visits to all households to seek verbal consent before collecting information on household members (name, sex and age details). Individuals who consent are offered the intervention i.e. the offer of HIV-testing and promotion of HIV prevention services and have basic health information recorded (past HIV test history, ART history etc.) onto a database. For individuals who self-report HIV-infection or who agree to test and are diagnosed HIV-positive, a written referral is made to link to the local government health centre (Figure 1.2). Men who are not already circumcised are advised to attend VMMC services. Patients with symptoms of TB or sexually transmitted infections are also referred accordingly (including collection of sputum samples for potential TB patients).

All HIV-infected individuals who are not stable on ART are followed-up to try to ensure linkage-to-care and provide support for ART. Individuals who were not previously encountered at home are also sought out through repeat home-visits to offer the intervention and try to ensure universal coverage of the intervention. All treatment services are provided at local government health facilities which were strengthened prior to trial preparation (to ensure supply chains etc.) but otherwise largely operate within the usual infrastructure of the local health system.

The primary outcome of HIV incidence will be measured in a Population Cohort (N=42,000) formed by 2,000 randomly selected adults from each community. This longitudinal cohort is being surveyed annually over 3 years and the primary outcome of HIV incidence over 36 months will be measured. A number of secondary outcomes are being measured to evaluate trial process measures and the impact, safety, cost and cost-effectiveness of the intervention.(40) Mathematical modelling is being done using trial data to project the longer term effects of the intervention. Qualitative research is embedded within the trial and case-control studies have been undertaken to examine factors associated with uptake of key interventions.

Figure 1.1 PopART Trial Schema

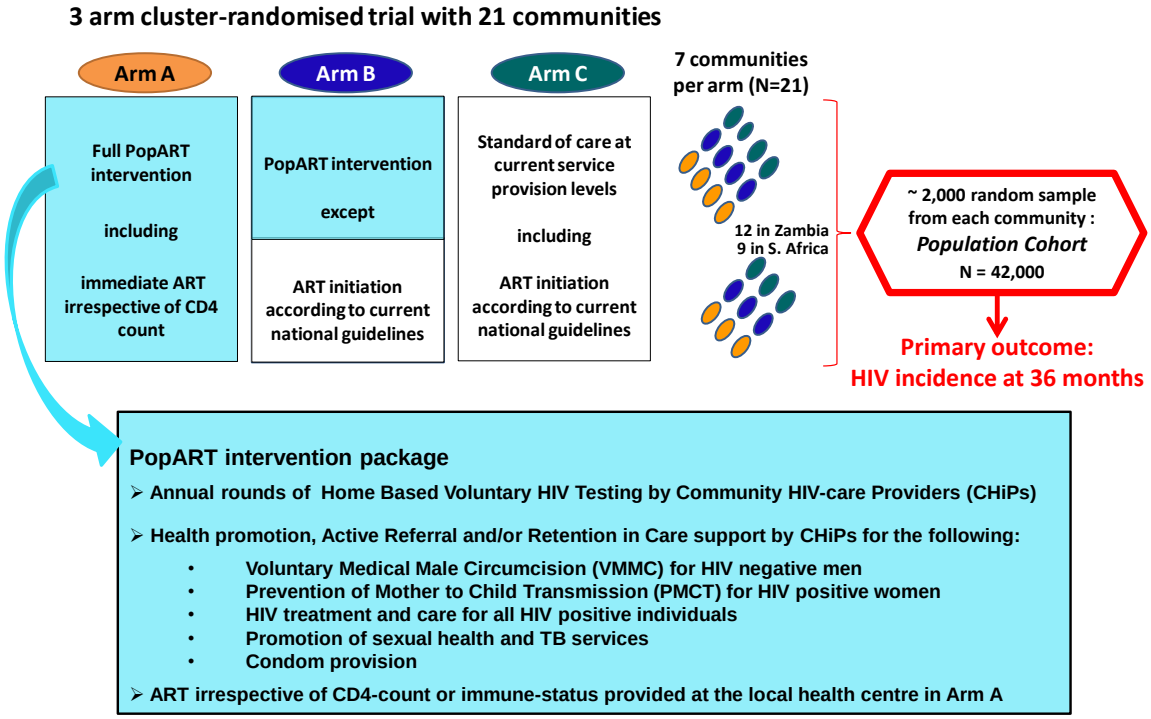
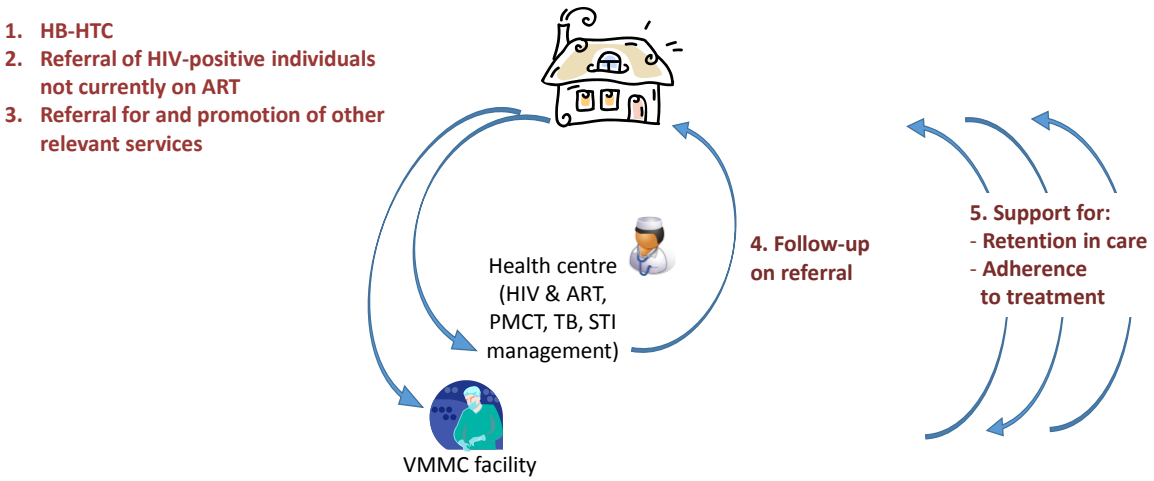


Figure 1.2 Schematic Overview of Household Visit



Intervention activities carried out by CHiPs in Arm A and B

1. HB-HTC for household members who accept CHiP intervention
2. Referral letter for timely linkage and ART initiation
3. Additional referral for other relevant prevention or treatment service (VMMC, ANC+PMCT, STI, TB) and distribution of condoms
4. Follow-up on referral
5. Support for retention in care – scheduled and tailored visits to patients to offer counselling, encourage adherence and attendance at health centre if medical attention is indicated

1.4 Key research components of PhD

1.4.1 Systematic review on home-based HIV testing and counselling

When the PhD was started in 2012, knowledge of HIV status in sub-Saharan Africa was low. The acceptability of home-based HIV counselling and testing (HB-HTC) as an approach to delivering wide-scale HIV testing held promise, but was not fully established. There was uncertainty about HB-HTC and concern that it may be poorly accepted or even harmful, partly owing to the stigma and discrimination around HIV/AIDS. During the period under study (2000-2012) testing was sometimes offered at the household but clients were required to attend the clinic to have post-test counselling to receive HIV results. We therefore explored both the proportion of acceptance of HB-HTC and of results received among those offered it. We also explored any potential social harm caused by HB-HTC and sought to summarise information on cost-effectiveness. (25) Studies from SSA which reported the proportion of individuals who accepted HIV testing, and who received results, out of those offered were included and meta-analysis performed to estimate acceptability of HB-HTC. The manuscript of this study is presented in Chapter 3.

1.4.2 Factors associated with the uptake of Home-Based Voluntary HIV Testing and Counselling during the first annual round of the PopART intervention - Case-control study 1

1.4.2.1 Rationale for Case-control study 1

HB-HTC is the key HIV testing intervention in PopART. It is provided in addition to other local efforts to increase knowledge of HIV status in the intervention communities.

While there are descriptive studies of acceptors of testing and HB-HTC, there is little analytical evidence specifically on non-acceptors of HB-HTC and their reasons to decline. There continue to be gaps in understanding of the structural, health systems and individual characteristics which affect the uptake of HB-HTC based on existing literature. Studies have demonstrated high acceptability of HB-HTC, but most of this evidence comes from conditions where ART eligibility criteria apply.(45, 46) It is important to identify the factors which influence the non-uptake and uptake of HB-HTC within the context of a UTT intervention as delivered in PopART. Research conducted on the uptake of HB-HTC during the first annual round of CHiPs HB-HTC could help to inform future rounds of HB-HTC in PopART. Mathematical modelling for the PopART trial suggests that the acceptability of HB-HTC is one of the important determinants of the size of the impact of the PopART intervention on HIV incidence (19). Exploring in detail the reasons that underpinned the achieved coverage of the intervention is critical to inform policy makers on the generalizability of the findings and help inform the future design and implementation of HB-HTC in sub-Saharan Africa. This case-control study

characterises in detail the factors associated with, and reported reasons for acceptance or non-acceptance of the HB-HTC component of the UTT strategy.

1.4.2.2 Study hypotheses

We hypothesised that there would be several factors including demographics, socio-economic circumstances, health and psychological status, alcohol and drug use, sexual behaviour, previous HIV testing, stigma and other related factors which would be different between non-acceptors and acceptors of HB-HTC in the first annual round of HB-HTC in PopART. Cases and controls were asked questions, to explore reasons for not testing and motivation to test, respectively. The questionnaire themes were tailored to provide a description of the case and control population (demographics, socio-economic circumstances etc.), as well as to identify if certain behaviours are more frequently associated with non-uptake of interventions. For instance, is the individual's satisfaction with their experience of the CHiPs team associated with uptake or non-uptake of testing with CHiPs? Such a finding would inform future training and conduct of the teams in order to improve uptake. Another example is that if an association is found between experience of intimate partner violence and non-uptake, this might inform us that associations between experience of violence and acceptance of health services (e.g. due to lack of autonomy to accept services for fear of consequences) require further investigation. Associations between various factors and uptake or non-uptake of CHiPs HB-HTC will be established, some of which may be modifiable to improve delivery of services.

This study is presented in Chapter 4.

1.4.3 Cascade of care following community-based HTC

A second systematic review was done to examine the effectiveness of community-based HIV-testing services (HTS), including home and mobile-based HIV-testing services (HB-/M-HTS), in improving care in SSA. While community-based approaches of testing have become established as effective means to increase knowledge of HIV status on a large scale, it was less clear whether they had an impact on enhancing access to timely HIV care. These approaches detect infected individuals earlier in the course of infection but individuals who feel well may not be ready to access care at health facilities even when provided with a diagnosis. While community-HTS reduces barriers for testing, the challenges associated with health facilities remain and individuals identified by community-HTS may be less likely and/or take longer to link-to-care. Studies from SSA between 2006-2016 which reported the proportion of individuals who link-to-care and/or initiate ART after detection of HIV through community-based testing were examined to determine the impact on uptake of the subsequent steps in the cascade of care. The manuscript of this study which has been submitted for publication is presented in Chapter 5.

1.4.4 Factors associated with timely initiation of immediate ART during the first annual round of the PopART trial - Case-control study 2

1.4.4.1 Rationale for Case-control Study 2

As “immediate treatment” is the linchpin of the PopART UTT intervention, understanding any barriers to wide-scale uptake will be crucial to understanding the trial findings. Although WHO guidelines now recommend ART irrespective of CD4-count for all PLWH, the provision of “immediate ART” for all HIV positive individuals represents largely uncharted territory.(7) As described in section 1.3, the UTT approach first seeks to test everyone in the community (universal testing) and refer them for care in the health-facility. This has to be followed by “timely-linkage-to-ART” (TLA) involving the 2 key steps of timely linkage-to-care (LTC) and ART initiation. A key challenge of TLA in UTT is that it seeks to achieve TLA among individuals who were detected with HIV in the community as part of universal testing, who may be asymptomatic and/or may not otherwise have sought HIV testing. Treatment readiness among such newly diagnosed individuals may be a challenge.

Qualitative data from in-depth interviews on initiation of ART before eligibility criteria are met suggest acceptability is high but much more data is needed. (47) Barriers have also been identified, including anxiety about life-long commitment and side effects of treatment, risks of drug resistance, fear of unwanted disclosure, perceived incompatibility with alcohol and resources required to obtain refills of drugs/continue in long-term care.(47) The loss from care of patients registered for care but not meeting ART eligibility criteria is now also well documented.(34, 35) The UTT approach removes the barrier imposed by the requirement to meet eligibility criteria.

Uptake of treatment in UTT would have to be wide-spread across sub-sets of the population with different socio-demographic and behavioural characteristics, for reduction of community-level HIV-incidence. The full impact of UTT on prevention would not be seen if sub-sets of the population were excluded or not engaging with the universal treatment intervention.

A case-control study was undertaken to identify the characteristics of those who do/do not link-to-care and start ART within 6 months of referral by the CHiPs upon detection of HIV (through HIV testing or self-report) in PopART during the first year of the intervention, and explored reasons for achieving TLA. The study seeks to address not only the treatment irrespective of immune-status or CD4 count aspect of UTT, but also the need to link-to-care, and for initiation of ART without delay, if the community level reduction in HIV incidence goal is to be achieved.

1.4.4.2 Study hypotheses

We hypothesised that there will be several factors including demographics, socio-economic circumstances, health and psychological status, alcohol and drug use, sexual behaviour, previous HIV

testing, stigma, perceptions about health services and other related factors which are different between achievers and non-achievers of TLA during the first year of the CHiP intervention in PopART Arm A. As in Case-control study 1, cases and controls were asked questions, to explore reasons for TLA and barriers against achieving TLA. The questionnaire themes were tailored to provide a description of the case and control population (demographics, socio-economic circumstances etc.), as well as to identify if certain behaviours are more frequently associated with non-uptake of interventions. For instance, is alcohol use negatively associated with TLA? Such a finding would help inform health providers that alcohol reduction services may be important to help towards enhancing TLA and universal treatment. Another example is that if an association is found between high risk sexual behaviour and non-uptake, it would inform us that a key population is not participating in the trial intervention and not benefiting from immediate treatment for prevention. This could have implications for onward HIV transmission in the communities, despite high uptake in the community overall.

This study is presented in Chapter 6.

1.5 Contribution to research

Both of the systematic reviews which were conducted for the PhD were conceived and led by me with oversight from Richard Hayes as my supervisor. I led on conceptualising the research questions, formulating search criteria and was the first reviewer on both papers. The systematic review and meta-analysis on HB-HTC was a collaboration with Nathan Ford and Rafael van den Burgh, who led on the meta-analysis component of the study and acted as second reviewer, respectively. The systematic review on the cascade of care following HB-HTC was a collaboration with Bernadette Hensen and Olivia Varsaneux, who jointly undertook the role of second independent reviewer for different components of the review (see Chapter 5). As first author, I co-ordinated the reviews, wrote the first drafts and led on revisions of subsequent drafts, including responding to journal reviewer comments on study manuscripts.

Although the case-control studies were nested within PopART and were subject to the regulatory requirements of the wider trial, the leadership of the studies was always my responsibility. The studies were identified as components which would contribute to my PhD from the beginning, when the PopART trial protocol was being written, and I was a member of the protocol writing team. With oversight from my supervisor who is Principal Investigator of the wider trial, I designed the case-control studies (including the questionnaires), wrote all study specific protocols and applied for regulatory approvals. Once approval was obtained, with senior input from in-country Principal Investigators (Helen Ayles, Zambia and Nulda Beyers, South Africa), I was responsible for staffing the

studies (conducting pre-employment interviews and training of field research assistants together with in-country management staff); collaborating with in-country data managers on programming of questionnaires and other aspects of data collection; and leading the initial data collection with field research managers and research assistants. I was in weekly contact with field research managers about challenges encountered by the teams, to offer support and guidance. I was responsible for the "real-time" monitoring of the electronic questionnaire data which was collected in the field and sent to me weekly/fortnightly. I performed the necessary data cleaning and carried out all statistical analyses, with advice from my supervisor and Sian Floyd (senior statistician on PopART). As with the systematic reviews, I wrote the first drafts and led on revisions of subsequent drafts of the study manuscripts.

1.6 Summary

In summary, the aim of this PhD is to improve understanding of the factors associated with the uptake of key interventions in UTT as delivered by the PopART trial. Two systematic reviews were done to inform and contextualise the primary research consisting of two case-control studies which were nested within the trial. The studies were done to enhance the understanding of factors associated with engagement in key steps in the cascade of HIV care during the first year of implementation of the trial. The findings will have immediate implications for the on-going implementation of activities at later stages of PopART. These studies will help to identify if individuals who do not engage in the interventions are also more likely to acquire/transmit HIV and affect the primary outcome of the trial (HIV incidence). This could provide data to inform mathematical models. Finally, it is hoped that this research will have longer term consequences for translating trial interventions into future policy and implementation.

1.7 References

1. UNAIDS. Global AIDS Update. http://wwwunaidsorg/en/resources/documents/2016/Global-AIDS-update-2016. 2016;Accessed on 13th June 2017.
2. United Nations General Assembly. Political Declaration on HIV/AIDS: Intensifying our Efforts to Eliminate HIV/AIDS. http://wwwunorg/ga/search/view_docasp?symbol=A/65/L77. 2011;Accessed on 26th August 2013.
3. Hankins CA, de Zalduondo BO. Combination prevention: a deeper understanding of effective HIV prevention. AIDS. 2010;24 Suppl 4:S70-80.
4. Pirrone V, Thakkar N, Jacobson JM, Wigdahl B, Krebs FC. Combinatorial approaches to the prevention and treatment of HIV-1 infection. Antimicrobial agents and chemotherapy. 2011;55(5):1831-42.
5. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The New England journal of medicine. 2015;373(9):795-807.
6. TEMPRANO ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.
7. World Health Organization. Guideline on when to start Antiretroviral therapy and on Pre-exposure Prophylaxis for HIV. http://appswhoint/iris/bitstream/10665/186275/1/9789241509565_engpdf?ua=1. 2015;Accessed on 26th February 2016.
8. Chasela CS, Hudgens MG, Jamieson DJ, Kayira D, Hosseinipour MC, Kourtis AP, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. The New England journal of medicine. 2010;362(24):2271-81.
9. de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. The Lancet infectious diseases. 2011;11(3):171-80.
10. Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. The New England journal of medicine. 2010;362(24):2282-94.
11. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Report on the global AIDS epidemic. http://wwwunaidsorg/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_enpdf. 2012;Accessed 30th January 2013.
12. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. The New England journal of medicine. 2000;342(13):921-9.
13. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. The Journal of infectious diseases. 2005;191(9):1403-9.
14. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009;23(11):1397-404.
15. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. The New England journal of medicine. 2016;375(9):830-9.
16. Rodger A, Cambiano V, Bruun T, Vernazza P, Collins S, Estrada V, et al. HIV transmission risk through condomless sex if the HIV positive partner is on suppressive ART: PARTNER study. 21st Conference on Retroviruses and Opportunistic Infections, Boston. 2014;Abstract 153LB.
17. Granich R, Crowley S, Vitoria M, Lo YR, Souteyrand Y, Dye C, et al. Highly active antiretroviral treatment for the prevention of HIV transmission. Journal of the International AIDS Society. 2010;13:1.

18. Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med. 2012;9(7):e1001245.
19. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. PloS one. 2014;9(1):e84511.
20. Garnett GP, Baggaley RF. Treating our way out of the HIV pandemic: could we, would we, should we? Lancet. 2009;373(9657):9-11.
21. De Cock KM, El-Sadr WM. When to Start ART in Africa - An Urgent Research Priority. The New England journal of medicine. 2013.
22. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013;339(6122):966-71.
23. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657):48-57.
24. El-Sadr WM, Affrunti M, Gamble T, Zerbe A. Antiretroviral therapy: a promising HIV prevention strategy? J Acquir Immune Defic Syndr. 2010;55 Suppl 2:S116-21.
25. Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N. Uptake of Home-Based Voluntary HIV Testing in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. PLoS Med. 2012;9(12):e1001351.
26. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health. 2010;15 Suppl 1:1-15.
27. Hayes R, Floyd S, Schaap A, Shanaube K, Bock P, Sabapathy K, et al. A universal testing and treatment intervention to improve HIV control: One-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. PLoS Med. 2017;14(5):e1002292.
28. Iwuji C, Orne-Gliemann J, Balestre E, Larmarange J, Thiebaut R, Tanser F, et al. The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. http://programmeaids2016org/Abstract/Abstract/10537. 2016;Accessed on 19th Oct 2016.
29. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. http://wwwunaidsorg/sites/default/files/media_asset/90-90-90_en_0pdf. 2014;Accessed on 11th January 2016.
30. McNairy ML, El-Sadr WM. The HIV care continuum: no partial credit given. AIDS. 2012;26(14):1735-8.
31. Mills EJ, Ford N. Home-based HIV counseling and testing as a gateway to earlier initiation of antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(2):282-4.
32. Lankowski AJ, Siedner MJ, Bangsberg DR, Tsai AC. Impact of geographic and transportation-related barriers on HIV outcomes in sub-Saharan Africa: a systematic review. AIDS and behavior. 2014;18(7):1199-223.
33. Wachira J, Kimaiyo S, Ndege S, Mamlin J, Braitstein P. What is the impact of home-based HIV counseling and testing on the clinical status of newly enrolled adults in a large HIV care program in Western Kenya? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(2):275-81.
34. Pati R, Lahuerta M, Elul B, Okamura M, Alvim MF, Schackman B, et al. Factors associated with loss to clinic among HIV patients not yet known to be eligible for antiretroviral therapy (ART) in Mozambique. Journal of the International AIDS Society. 2013;16:18490.

35. Bastard M, Nicolay N, Szumilin E, Balkan S, Poulet E, Pujades-Rodriguez M. Adults receiving HIV care before the start of antiretroviral therapy in sub-Saharan Africa: patient outcomes and associated risk factors. J Acquir Immune Defic Syndr. 2013;64(5):455-63.
36. Gari S, Martin-Hilber A, Malungo JR, Musheke M, Merten S. Sex differentials in the uptake of antiretroviral treatment in Zambia. AIDS care. 2014;26(10):1258-62.
37. Iwuji CC, Orne-Gliemann J, Larmarange J, Okesola N, Tanser F, Thiebaut R, et al. Uptake of Home-Based HIV Testing, Linkage to Care, and Community Attitudes about ART in Rural KwaZulu-Natal, South Africa: Descriptive Results from the First Phase of the ANRS 12249 TasP Cluster-Randomised Trial. PLoS Med. 2016;13(8):e1002107.
38. Petersen M, Balzer L, Kwarsiima D, Sang N, Chamie G, Ayieko J, et al. SEARCH test and treat study in Uganda and Kenya exceeds the UNAIDS 90-90-90 cascade target by achieving 81% population-level viral suppression after 2 years. AIDS 2016, Durban, South Africa. 2016;Abstract WEAC0106LB(Accessed on 18th June 2017).
39. Gaolathe T, Wirth KE, Holme MP, Makhema J, Moyo S, Chakalisa U, et al. Botswana's progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey. Lancet HIV. 2016;3(5):e221-30.
40. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.
41. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2(11):e298.
42. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369(9562):643-56.
43. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369(9562):657-66.
44. HPTN 071 Protocol Team. HPTN 071 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa. http://wwwhptnorg/research_studies/hptn071asp. 2012.
45. van Rooyen H, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2013;64(1):e1-8.
46. Tumwesigye E, Wana G, Kasasa S, Muganzi E, Nuwaha F. High uptake of home-based, district-wide, HIV counseling and testing in Uganda. AIDS Patient Care STDS. 2010;24(11):735-41.
47. Logan A, Plank R, Bogart L, Moloi K, Maotonyane K, Bussmann H, et al. Acceptability of early initiation of antiretrovirals for treatment as prevention among HIV-infected persons in Mochudi, Botswana. 7th Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, Malaysia. 2013; MOAC0204 - Oral Abstract Session (Accessed 14th November 2013).

Chapter 2: Case-control study methods

Outline of chapter

As described, two case-control studies were conducted as part of the PhD to evaluate the 2 key elements of the UTT model – universal testing and universal treatment. This chapter describes the methods used in the design, implementation and analysis of those studies.

2.1. Factors associated with the uptake and non-uptake of Home-Based Voluntary HIV Testing and Counselling during the first annual round of the PopART intervention - Case-Control study 1 (CC1)

2.1.1 CC1 objectives

i. To identify differences between non-acceptors and acceptors of HB-HTC during the first annual round of HB-HTC in PopART.

ii. To identify reasons for non-acceptance of HB-HTC during the first annual round of HB-HTC in PopART.

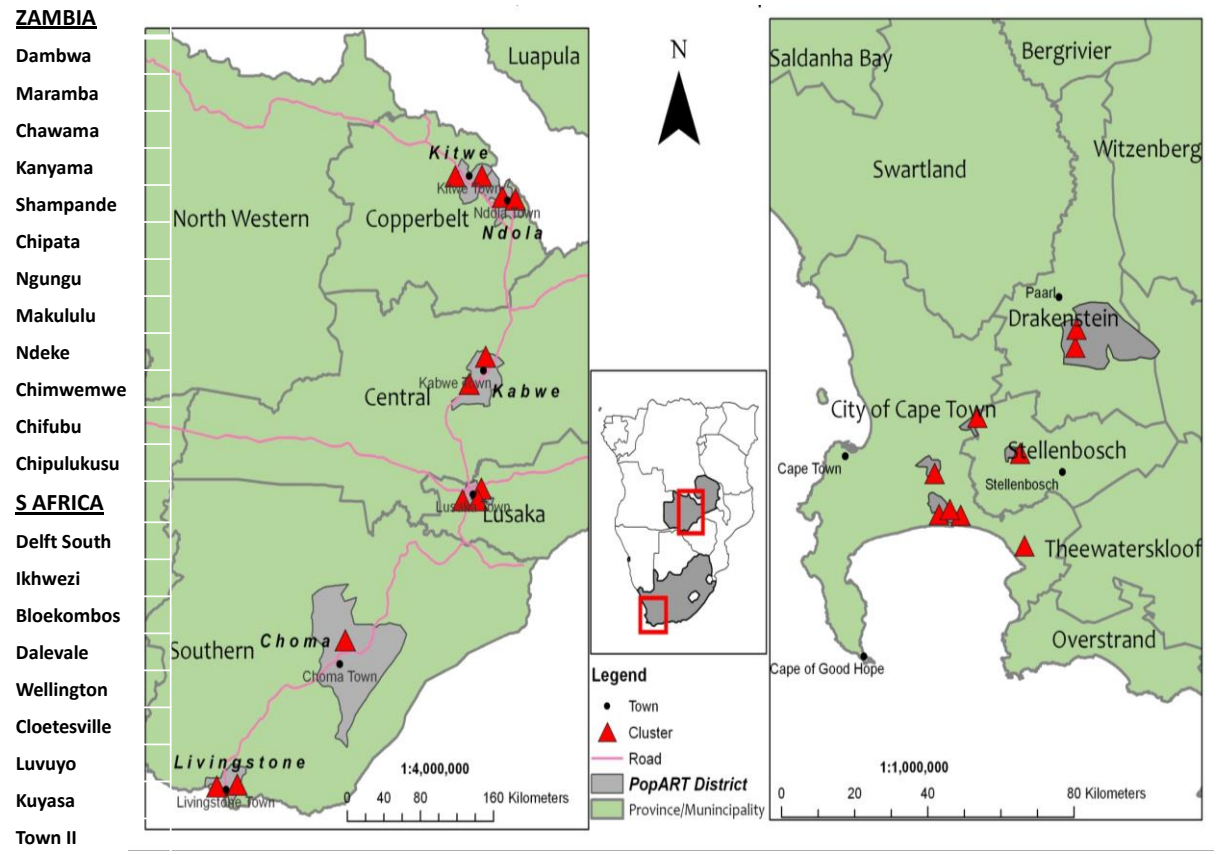
Achieving the above objectives could help to modify aspects of delivery of the HB-HTC intervention that may be associated with non-acceptance.

2.1.2 CC1 Study design

A case-control study was planned to study the factors associated with uptake of HB-HTC in PopART (Arms A and B) – Case-control Study 1. Given the evidence that HB-HTC is likely to receive high acceptance, non-acceptance was expected to be a relatively infrequent event. A case-control design was chosen because it is suited to explore infrequent outcomes and multiple exposures in an efficient manner.

2.1.3 CC1 Study setting

Figure 2.1 List and location of the 21 PopART trial communities



Source: HPTN 071 (PopART) Trial Protocol Version 1.0

The 21 communities involved in PopART are shown above (12 in Zambia and 9 in South Africa). They vary in size from 21,386 to 166,251 total population size (an average of 57,828 or 66,864 in Zambia and 45,780 in South Africa) and adult HIV prevalence estimates range from 13-26%. They are all urban or peri-urban sites. The source population for CC1 was the populations of all 14 communities in Zambia and South Africa allocated to Arms A and B in PopART.

2.1.4 Inclusion and exclusion criteria of CC1 study participants

Inclusion Criteria Case-Control Study 1

- At least 18 years of age
- Able and willing to provide informed consent
- Resident in the cluster during the first round of testing
- Visited by a CHiP team and offered testing during the first round of home-based testing

Exclusion Criteria Case-Control Study 1

- Individuals belonging to the *Population Cohort* of the trial or other case-control studies
- Individuals known to be HIV-infected after testing elsewhere.

As shown above, community members who were at least 18 years old and able and willing to provide informed consent were eligible for inclusion in Case-control study 1. Their residence in the community during the first PopART annual round was recorded in the CHiPs electronic register along with whether face-to-face contact was made during delivery of the intervention. Acceptance of the intervention involved consent to basic data being collected and receiving health information provided by the CHiPs. Community members may have chosen to accept the intervention but not accepted HB-HTC. To be included in the case-control study, the individual must have accepted the CHiP intervention (in order to be offered HB-HTC). Those who also accepted HB-HTC were eligible to be controls and those who did not accept the HB-HTC component of the intervention were potential cases.

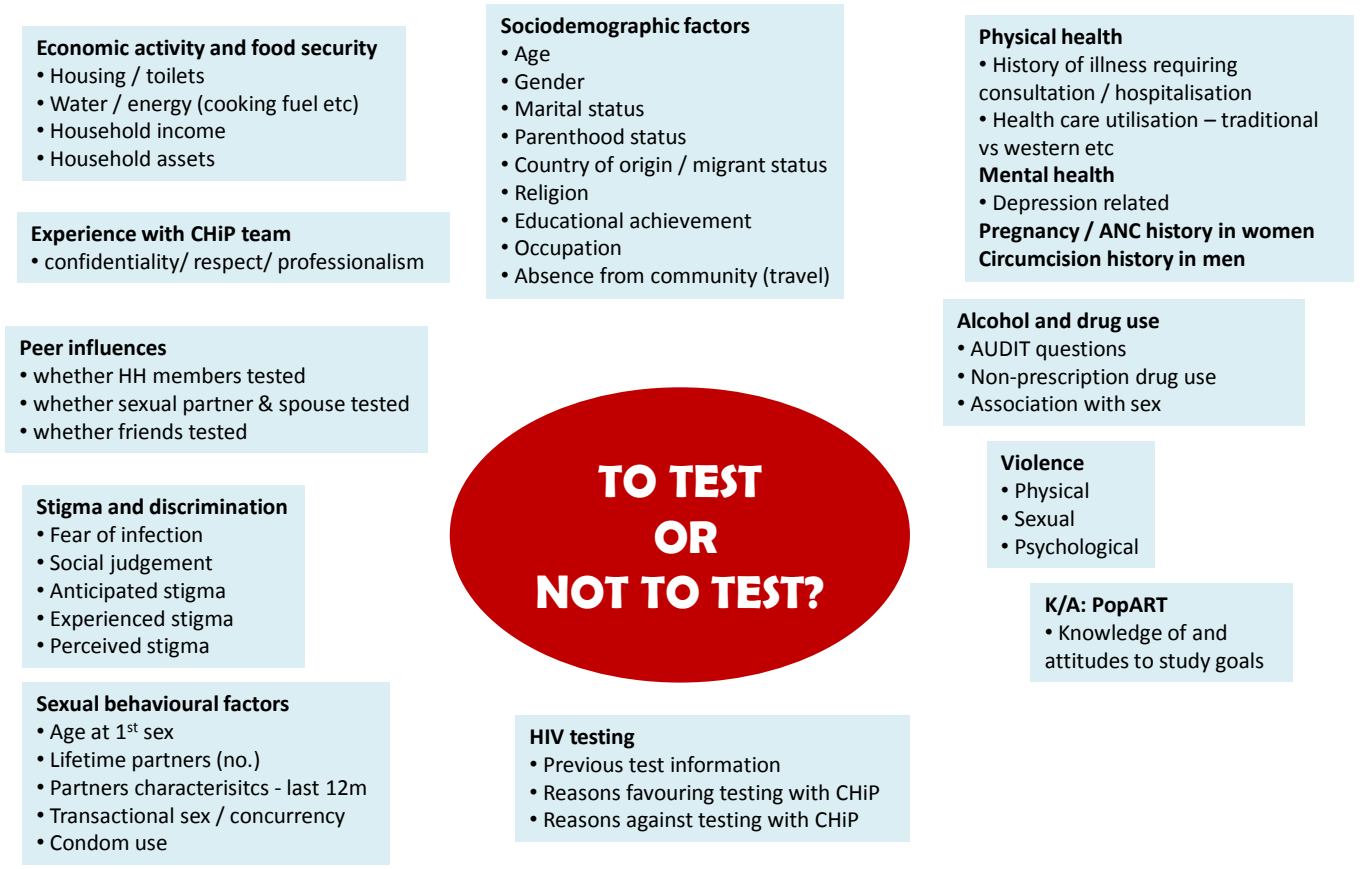
Members of the PC were excluded to minimise the Hawthorne effect on the main trial research cohort. Community members who self-reported as already known to be HIV-infected were also excluded (as they were not routinely offered HIV testing - previously known HIV-positive status was recorded in the electronic register). No proof of HIV-positive status (among those self-reporting) was sought as it was thought quite unlikely that individuals would claim to be HIV-positive just to avoid study participation.

Inclusion and exclusion criteria were determined from information in the CHiP database in the first instance (e.g.. residence in the cluster during the first annual round or self-report of HIV positive status) and completed by the CC RAs at the time of approach for study participation, for information which was not available from the CHiP database (e.g.. ability/willingness to provide informed consent or prior inclusion into the Population Cohort).

2.1.5 Factors which may influence non-uptake/uptake of HB-HTC

Shown in Figure 2.2 are the factors which were expected to influence the non-uptake and uptake of HB-HTC which were explored by the standardised questionnaires in the study. It was expected that some associations would be causal while other factors would co-exist and have a causal factor in common. Several factors may be inter-related or have a confounding effect on other associations. These elements were important to explore in order to improve understanding of non-engagement with the HB-HTC intervention and the resultant impact of the PopART package on HIV incidence reduction.

Figure 2.2 Factors which may influence non-uptake/uptake of HB-HTC



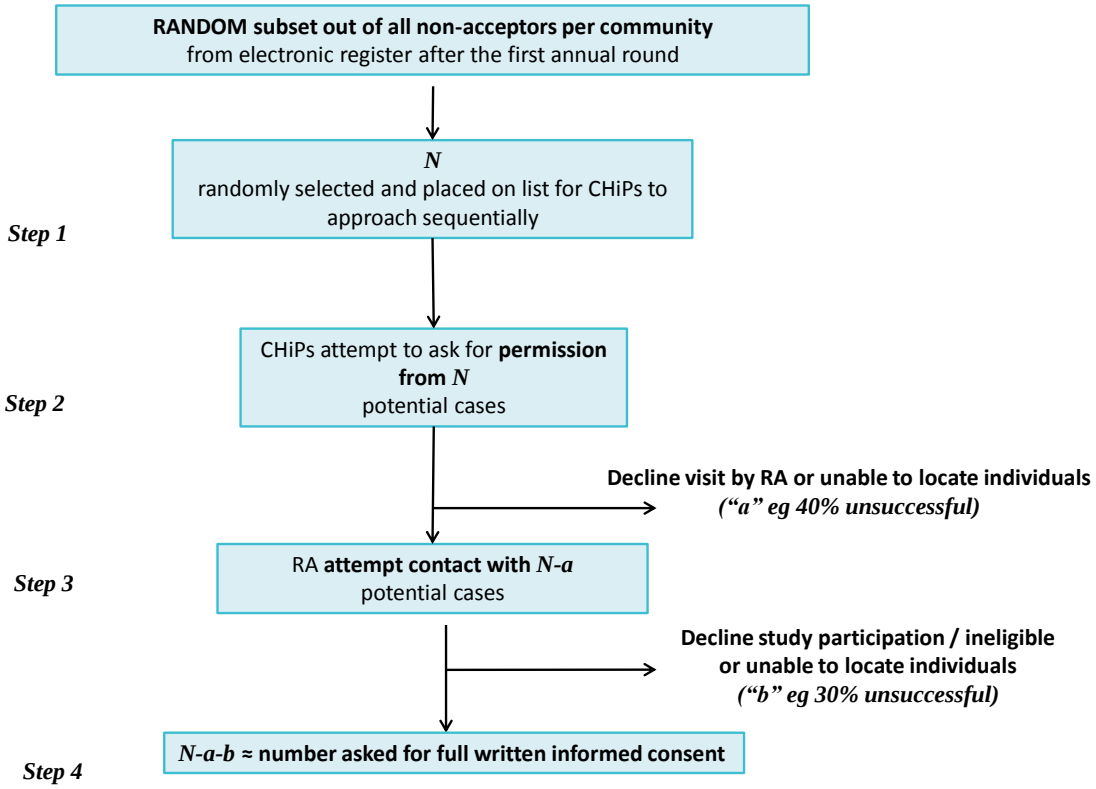
2.1.6 CC1 Study procedures

2.1.6.1 Selection of cases

Definition of cases in Case-control study 1: a random sample of non-acceptors of HB-HTC offered by CHiPs in Arms A and B of the PopART trial during the first annual round of the intervention. Non-acceptance was defined as such after the end of the CHiP annual round of initial visits to offer the intervention. By design this meant that community members who were absent from the household when a CHiP team visited and those who declined to be interviewed by the CHiP (both after repeated attempts), were excluded. This was a necessary compromise for feasibility of study conduct and allow direct comparison between those who accepted and those who declined - both after being offered HB-HTC.

It is also acknowledged that between the CHiPs home-visit and the time of the study, some individuals may have had an HIV test (by other means of testing), who had declined HB-HTC when offered by CHiPs during the annual round. However, provided a community-member met the afore-mentioned inclusion and exclusion criteria, and non-acceptance of the HIV test was recorded in the CHiP EDC register at the time of random selection, the individual was eligible to be a case in the study.

Figure 2.3 Selection of cases – at the end of the first annual round of HB-HTC



As shown in Figure 2.3 above, approximately 400 cases (200 men and 200 women) were to be included in the study (see Section 2.5 on Sample size calculations) – amounting to approximately 30 cases per community (7 Arm A and 7 Arm B communities). The following describes the planned recruitment strategy. Chapter 4 presents the actual numbers recruited into CC1.

The CHiP Electronic Data Capture (EDC) register of individuals in PopART Arm A and B communities provided the starting point for selection of non-acceptors of HB-HTC (amongst those offered HB-HTC during the first year of the trial intervention). From all non-acceptors in the register, a higher number than was required for inclusion in the study was randomly selected (N = 70 per community). This larger number allowed for failures to locate individuals and/or refusals to participate in the study. It was estimated as the number needed after back calculation from the final number needed (30 cases and 30 controls per community), as described below. The ID numbers of 70 randomly selected non-acceptors were placed in a random order, on a sequential list of potential subjects as shown in Step 1 above.

In Step 2, CHiPs visited each of the non-acceptors on the list for the CC study. They sought to obtain verbal permission from individuals for their details to be passed on to the Case-control study Research Assistants (RAs). It was anticipated that a number of individuals would not be located

when the CHiPs returned to request permission or would decline permission for details to be passed on to an RA for any further discussion regarding study participation ("a" – estimated to be approximately 40% based on experience from the Population Cohort enrolment process). The permission requested by the CHiPs was to enable them to pass on the individual's name, gender, age/date of birth and address - to facilitate approach of the client by a study RA. Note, no information about HB-HTC acceptance/ non-acceptance or any details gathered during the CHiP intervention were conveyed to the RAs, and clients were explicitly informed of this by the CHiPs. Shown in Appendix 2 is the Information sheet and verbal consent document used by the CHiPs in Zambia (with an alternative country-specific version used for SA).

In Step 3, the study RAs attempted to approach the individuals who had given verbal permission ("N-a" who agreed when asked by CHiPs). Again at this stage it was anticipated that some individuals would not be located or they may decline ("b" – estimated to be approximately 30%). This proportion was smaller than "a" as these were individuals who had already agreed when asked by the CHiPs at Step 2 (just a short time earlier). In Step 4, all clients who had agreed to study participation (N-a-b i.e. ~30 individuals) were provided with detailed study information and written informed consent for study participation was requested.

Note, all N-a-b individuals were to be included in the study if they consented, even if the number was higher than the required ~30 participants per community as defined by the sample size calculations. If the number who consented was much less than required, then the steps described above would be repeated, with a fresh random sample of participants selected from the CHiP register. On this occasion N, a and b would be estimated based on the actual response rates at the initial stage, separately for men and women, with the aim of reaching the required sample size in total. The process outlined above was to be undertaken with a view to minimising selection bias, which may otherwise occur if a more convenient sampling approach was taken. We wanted to ensure the sample of non-acceptors was as representative of the overall pool of non-acceptors as possible. The study was planned to take place at the end of the first annual round of HB-HTC.

The above description outlines how cases were selected. The same process was undertaken for controls, simultaneously. When CHiPs approached non-acceptors for study participation, they may on that occasion have re-offered HB-HTC – for service delivery purposes and in keeping with their ethical duty to clients. Even if an individual now took up HB-HTC, his/her uptake status at the time of random selection was used to define case vs control status. In addition, the research team was kept blind to the acceptance/non-acceptance status of potential participants when they approached them for informed consent.

2.1.6.2 Selection of controls

The purpose of having controls in this study was to have a representative sample of individuals who accepted HB-HTC for comparison with those who did not accept.

Controls in Case-control study 1 were defined as a subset of acceptors of HB-HTC which was offered by Community HIV-care providers (CHiPs) in Arms A and B of the PopART trial in the first annual round of HB-HTC. Acceptance was defined as such if HB-HTC was accepted before the end of the CHiP annual round.

The inclusion and exclusion criteria were the same as for cases. The controls for Case-control study 1 were selected through a similar process as described for the cases, simultaneously with the case selection process and beginning with the approach by CHiPs of a random subset of individuals who accepted HB-HTC, aiming for inclusion in the study of ~30 controls per community. The ratio of cases to controls would be approximately 1:1, and among each of cases and controls the ratio of men to women would be approximately 1:1 because the random sample would be selected stratified on gender. They would also be frequency matched on the communities in which they resided. All the ratios would be approximate dependent on what proportion of the N initially selected eventually accepted study participation among cases vs controls, men vs women and by community, with the goal of achieving the required total number in the study of ~400 cases and ~400 controls as guided by the sample size estimates. Chapters 4 and 6 present the actual numbers recruited into the CC1 and CC2, respectively.

2.1.7 CC1 Study questionnaire

Research assistants conducted participant interviews for Case-control study 1 at approximately the end of the first annual round of HB-HTC in PopART. Standardised questionnaires which explored potential factors which may be associated with non-uptake / uptake of HB-HTC in PopART were administered by the RAs (Figure 2.2). Written informed consent was obtained and questionnaires administered during an interview lasting 1-1.5 hour total duration, at the household or a preferred location of the participant. Shown in Appendix 3 is the Information and sheet and informed consent form for South Africa (with an alternative country-specific version used for Zambia) and Appendix 4 displays the CC1 study questionnaire. Data were captured using electronic capture devices.

2.2. Factors associated with timely initiation of immediate ART during the first annual round of the PopART trial - Case-Control study 2 (CC2)

2.2.1 CC2 Study objectives

i. To identify differences between those who do and do not achieve timely linkage-to-care and ART initiation in Arm A during the first year of the PopART intervention.

ii. To identify reasons for failure to achieve timely linkage-to-care and ART initiation in Arm A during the first year of the PopART intervention.

Achieving the above objectives could help to ensure the PopART intervention succeeds in achieving UTT.

2.2.2 CC2 Study design

A case-control study was planned to study the factors associated with timely linkage and uptake of immediate ART in PopART (Arm A) during the first year of the trial – Case-control Study 2. As in CC1, this design was chosen because it is suited to explore infrequent outcomes and multiple exposures in an efficient manner. As it turned out failure to initiate ART in a timely manner was not infrequent. The choice of design was still relevant however as it enabled to the examination of multiple exposures. The source population for this study was the population of all 7 sites allocated to Arm A in PopART, in Zambia and South Africa.

2.2.3 CC2 Study setting

CC2 was conducted in 7 PopART Arm A communities in Zambia and South Africa, (4 in Zambia and 3 in South Africa) where immediate ART was provided from the launch of the trial (Figure 1.1). Arm B and C communities were providing treatment according to national guidelines with eligibility criteria and were therefore not included in this study.

2.2.4 Inclusion and exclusion criteria of CC2 study participants

Inclusion Criteria Case-Control Study 2

- At least 18 years of age
- Able and willing to provide informed consent
- Resident in the cluster during the first round of testing
- Tested HIV-infected in CHiP home-based testing, or HIV-infected and disclosed that they were previously diagnosed as HIV-infected to CHiP team

Exclusion Criteria Case-Control Study 2

- Individuals belonging to the *Population Cohort* or other case-control studies
- HIV-infected individuals already on ART when initially seen by the CHiPs

As shown above, community members who were at least 18 years old and able and willing to provide informed consent were eligible for inclusion in Case-control study 2. Residence in the community during the first PopART annual round was recorded in the CHiPs electronic register. The individual had to have been visited by a CHiP team, consented to the CHiP intervention, and identified as HIV-positive – either upon testing positive from CHiP HB-HTC or self-report of being HIV-positive but not on treatment. Such individuals would then have been referred to the health-facility for HIV care and immediate ART.

As for CC1, members of the PC were excluded to minimise the Hawthorne effect on the main trial research cohort. Participants of CC1 were also excluded to minimise research fatigue and because there were overlaps in the CC1 and CC2 questionnaire which could have led to reporting bias. Community members who self-reported as already known to be on ART when initially seen by the CHiPs were also excluded.

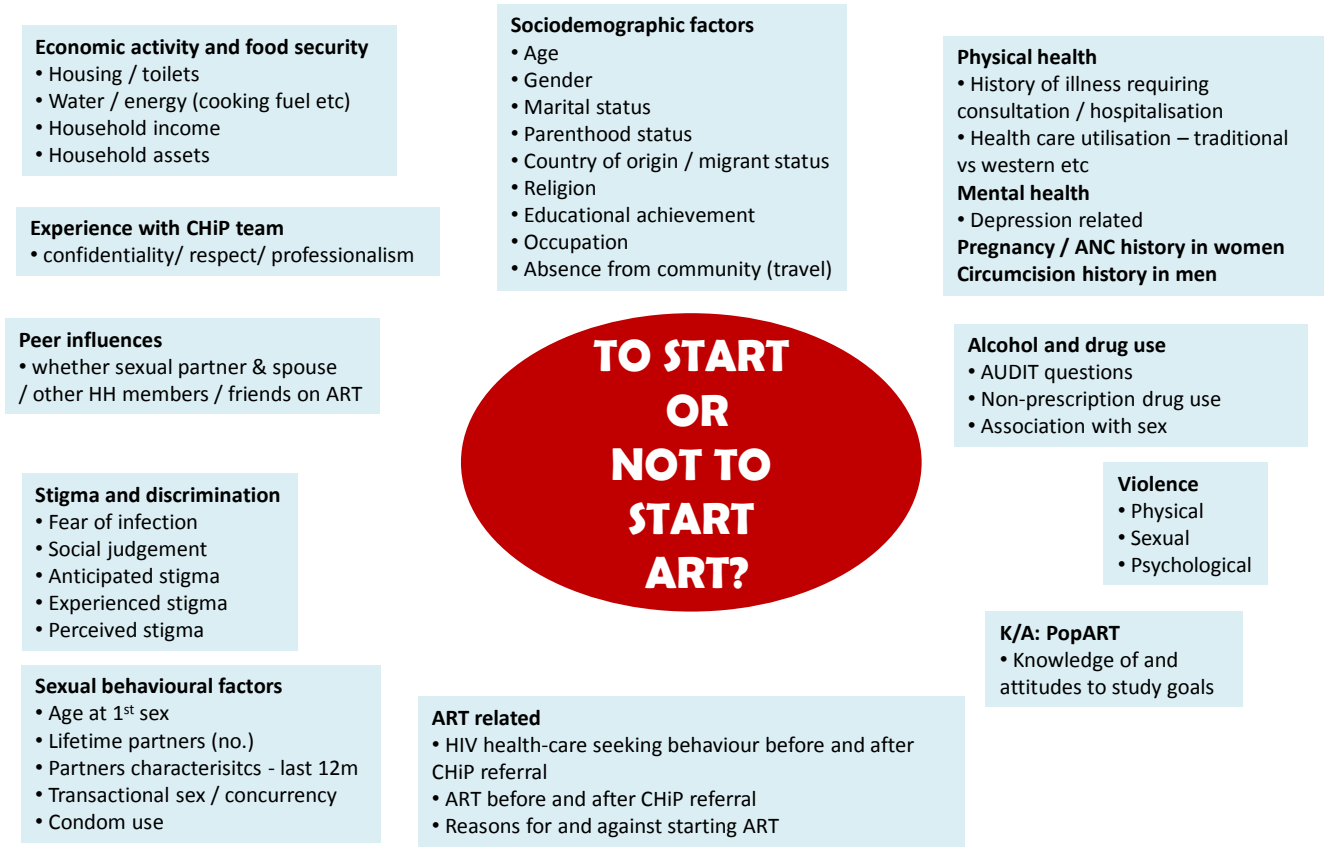
Inclusion and exclusion criteria were determined from information in the CHiP database in the first instance (e.g. HIV-positive status or information that client already on ART) and completed by the CC RAs at the time of approach for study participation, for information which was not available from the CHiP database (e.g.. ability/willingness to provide informed consent or prior participation in CC1).

2.2.5 Factors which may influence non-uptake/uptake of immediate ART

Shown in Figure 2.4 are the factors which were expected to influence TLA which were explored by the standardised questionnaires in the study. The evidence on factors associated with TLA are important to identify in the context of PopART to discover both what is and what is not associated with non-uptake. It was expected that some associations would be causal while others would co-

exist and have a causal factor in common. Several factors may be inter-related or confound other associations. These elements were important to explore in order to improve understanding of non-engagement with the immediate ART intervention and the resultant impact of the PopART package on HIV incidence reduction.

Figure 2.4 Factors which may influence non-uptake/uptake of immediate ART



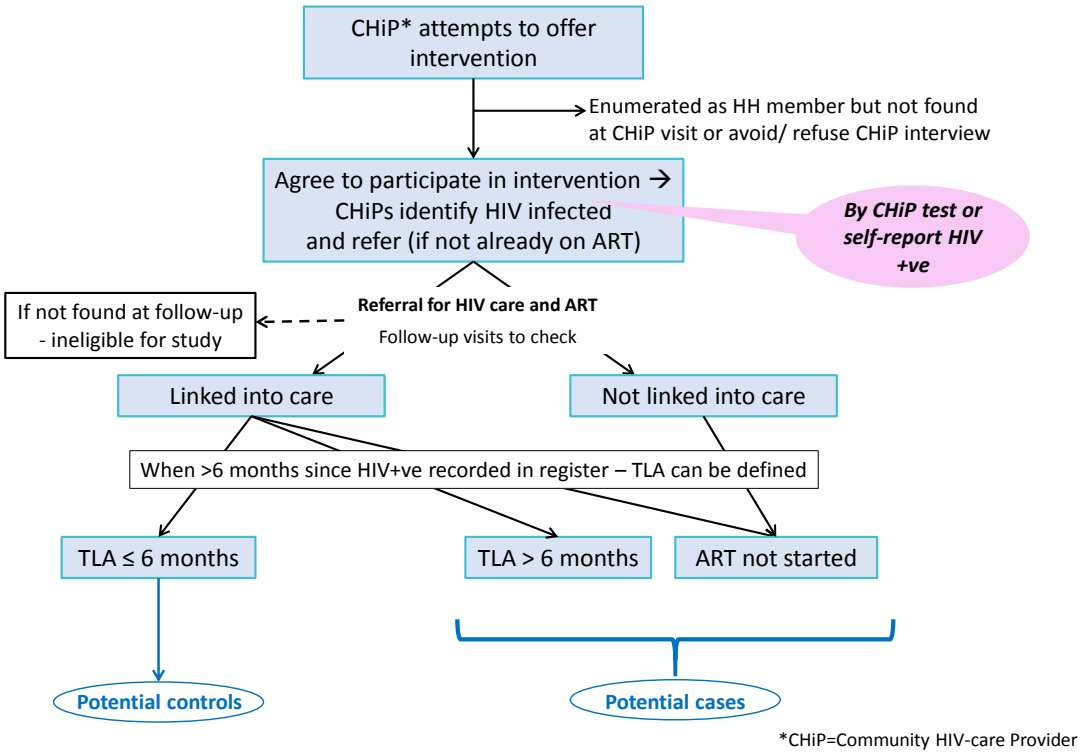
2.2.6 CC2 Study procedures

2.2.6.1 Selection of cases

Cases in Case-control study 2 were defined as a subset of randomly selected individuals who did not link-to-care and initiate ART within 6 months of HIV positive status being recorded in the CHiPs electronic register in Arm A, during the first year of PopART (see Figure 2.5).

A timeline of 6 months was used to define "immediate" ART. This was revised from an earlier cut-off of 3 months when it was observed in the intervention process data that too few PLWH had initiated within this time. The majority of those who initiated ART (in the first year) had done so by six-months and this time-point was chosen instead. In order to achieve HIV incidence reduction with UTT in PopART, timely linkage and ART initiation is the goal. As such, provided an HIV positive community-member met the afore-mentioned inclusion and exclusion criteria, and was recorded in the CHiP electronic register as not having initiated ART within 6 months, the individual was eligible to be a case in the study, just as if ART was not initiated at all. Whether or not TLA had been achieved was determined at follow-up visits which were routinely done by CHiPs for PLWH who had been referred for TLA. Outcomes were recorded in the CHiP register. Individuals who were not contactable at follow-up to obtain information on ART initiation status were therefore not included as potential candidates for the study (Figure 2.5).

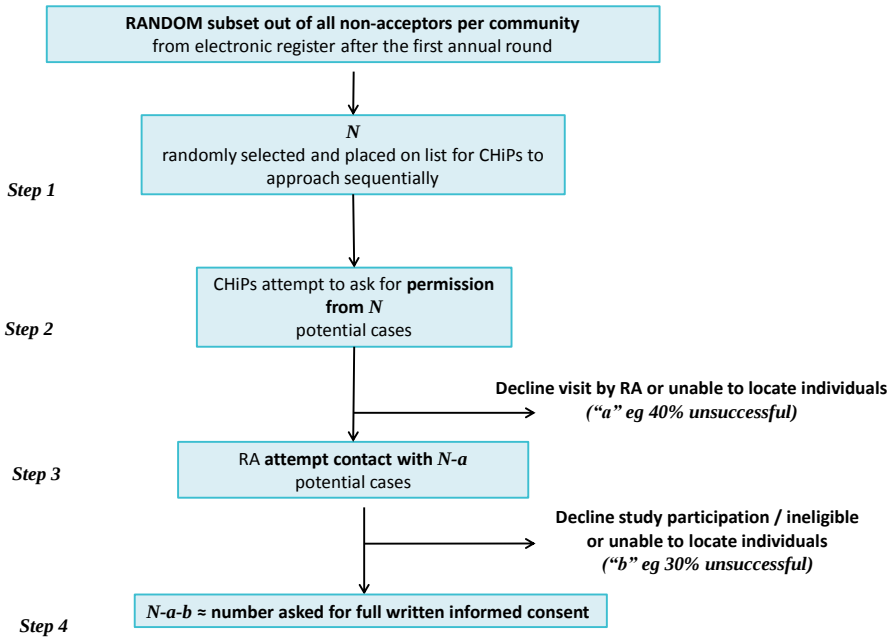
Figure 2.5 Identification of individuals who did and did not achieve TLA



*CHiP=Community HIV-care Provider

Shown in Figure 2.6 below was the process of selection of cases, after they had been identified as eligible for random selection from the CHiP electronic register i.e. as potential cases.

Figure 2.6 Selection of cases



As shown in Figure 2.5, approximately 400 cases (200 men and 200 women) were to be included in the study (see Section 2.5 on Sample size calculations) – amounting to approximately 60 cases per community (7 Arm A communities). The following describes the planned recruitment strategy. Chapter 6 presents the actual numbers recruited into CC2.

The CHiP electronic register of individuals in PopART Arm A communities provided the starting point for selection of those who had not achieved TLA (amongst those referred by CHiPs) during the first year of the intervention. A higher number than was required for inclusion in the study was randomly selected (N = 140 per community). It was estimated as the number needed after back calculation from the final number needed (60 cases and 60 controls per community), as described below. This larger number allowed for failures to locate individuals and/or refusals to participate in the study. The ID numbers of 140 randomly selected potential cases were placed in a random order, on a sequential list of potential subjects as shown in Step 1 above.

In Step 2, CHiPs visited each of those who had not achieved TLA on the list. They sought to obtain verbal permission from individuals for their details to be passed on to the case-control study

Research Assistants (RAs). It was anticipated that a number of individuals would not be located when the CHiPs returned to request permission or would decline permission for details to be passed on to an RA for any further discussion regarding study participation ("a" – was estimated to be approximately 40% based on the experience of enrolment into the Population Cohort and CC1). The permission sought by the CHiPs was to enable them to pass on the individual's name, gender, age and address - to facilitate approach of the client by a study RA. No information about ART initiation or any details gathered during the CHiP intervention were conveyed except the fact that the individual had been referred for HIV care, and clients were explicitly informed of this when permission was requested.

As in CC1 in Step 3, the study RAs attempted to approach the individuals who had given verbal permission ("N-a" individuals who agreed when asked by CHiPs). At this stage it was anticipated that some individuals (who previously assented to CHiPs) would not be located or may decline study participation at this stage ("b" – estimated to be approximately 30% further unsuccessful attempts). This proportion was smaller than "a" as these were individuals who had already agreed when asked by the CHiPs at Step 2 (just a short time earlier). In Step 4, all clients who had agreed to study participation ("N-a-b" ≈ 60 individuals) were provided with detailed study information and written informed consent for study participation was requested.

Note, all "N-a-b" individuals were to be included in the study if they consented, even if the number was much higher than the required ~60 participants per community as defined by the sample size calculations. If the number who consented was much less than required, then the steps described above were to be repeated, with a fresh random sample of participants selected from the CHiP register. On this occasion N, a and b would be estimated based on the actual response rates at the initial stage, separately for men and women, with the aim of reaching the required sample size in total. The process outlined above was to be undertaken with a view to minimising selection bias, which would otherwise occur if a more convenient sampling approach was taken. This was to ensure the sample of non-acceptors was as representative of the overall pool of non-initiators as possible. The study was to take place at the end of the first CHiP annual round and be restricted to community members who had at least 6 months to start ART since referral by a CHiP.

The above description outlines how cases were selected, but the same process was undertaken for controls, simultaneously. When CHiPs approached non-acceptors for study participation, they may on that occasion have re-referred participants who had not yet started treatment – for service delivery purposes and in keeping with their ethical duty to clients. Even if an individual now went on to start ART, his/her ART` initiation status at the time of random selection was used to define case vs

control status. In addition, the research team were kept blind to the ART status of potential participants when they approached them for informed consent.

2.2.6.2 Selection of controls

The purpose of having controls in this study was to have a representative sample of individuals who achieved TLA for comparison with those who did not.

Controls in Case-control study 2 were defined as a subset of individuals who linked-to-care and initiated ART within 6 months of HIV test positive status being recorded in the CHiP electronic register in Arm A, after a year of the PopART intervention.

The inclusion and exclusion criteria were the same as for cases. The controls for Case-control study 2 were selected through a similar process as described for the cases, simultaneously with the case selection process and beginning with the approach by CHiPs of a random subset of individuals who linked-to-care and initiated ART within 6 months, aiming for inclusion in the study of ~60 controls per community. The ratio of cases to controls was to be approximately 1:1, and among each of cases and controls the ratio of men to women would be approximately 1:1 because the random sample would be selected stratified on gender, and they would be frequency matched on the communities in which they resided. All the ratios would be approximate dependent on what proportion of the N initially selected eventually accepted study participation among cases vs controls, men vs women and by community, with the goal of achieving the required total number in the study of ~400 cases and ~400 controls as guided by the sample size estimates.

2.2.7 CC2 Study questionnaire

Research assistants conducted participant interviews for Case-control study 2 at approximately the end of the first annual round. Standardised questionnaires which explored potential factors which may be associated with achieving/not achieving TLA (Figure 2.4) were administered by the RAs. Written informed consent was obtained and questionnaires administered during an interview lasting 1-1.5 hour total duration, at the household or a preferred location of the participant. Shown in Appendix 5 is the Information sheet and informed consent form for South Africa (with an alternative country-specific version used for Zambia) and Appendix 6 displays the CC1 study questionnaire. Data were captured using electronic capture devices.

2.3. Recruitment, training and field preparation for case-control studies

Prior to the launch of the CC studies new staff were recruited. One team per community were recruited. A team consisted of two RAs, one woman and one man if possible, who spoke the most prevalent language of the community they worked in or so that each RA spoke one local language

each (e.g. in some South African communities it was important that there was one Xhosa and one Afrikaans speaking RA). All RAs were also fluent in written and spoken English which was the language of the questionnaires. In addition to the RAs, a study manager was appointed in each country (from existing staff in SA and newly recruited in Zambia) to monitor the quality of day to day study progress, liaise with other colleagues in-country (e.g. CHiP teams, senior supervisory staff, data management colleagues etc.) and to provide feedback to the in-country PI and to me as study PI.

Immediately prior to launch of the respective study in each country, trainings for the RAs were conducted which involved providing background for questionnaire themes, role-play and practice in administering questionnaires, and training on the use of electronic devices. Pilots were carried out with volunteer community members and minor changes made to the questionnaire / programming of electronic device, as needed. All staff underwent Good Clinical Practice and Human Subjects Protection training in line with the respective country's requirements.

The CHiPs teams in all Arm A and Arm B communities where the studies were to be conducted were also visited by the in-country CC study manger and me as study PI. The CC studies were introduced and CHiPs' role in requesting permission from their clients for contact details to be shared with the CC RAs was described.

2.4. Data management of case-control studies

2.4.1 Routine data management

All data about participants from both CC1 and CC2 were stored after removing identifying information so that data could not be readily traced back to individual community members. In-country data management was done in each respective country by local data managers. Data were sent to me as the study PI at regular intervals for monitoring and feedback to in-country research teams.

2.4.2 Data irregularities in South African CC1 data

During routine data monitoring I noted irregularities in the data which led to internal investigations being carried out in cooperation with the in-country study team. The findings indicated strong evidence of data fabrication in two communities (19 and 16) and limited evidence of data fabrication in one further community (14) - in South Africa. There was no clear evidence of data fabrication in the three remaining communities (13, 18 and 20) in South Africa, or in Zambia. These findings were supported by subsequent external investigations. Corrective and preventive actions were instituted, relating to human resource management, field work implementation and management including re-

training on research integrity. The study team formulated a plan to verify data and retain data that could be verified.

In summary, the CC1 Data Verification plan was to discard all data from Community 19 in South Africa and to omit this community from the study (due to the scale of data fabrication there). In the other five communities, we carried out a rigorous verification exercise for each participant and retained data if the identity of the participant and the responses provided in the study were verified.

The CC1 Data Verification plan was approved by both the South African and LSHTM ethics committees and the process was undertaken in early March 2016. Shown in Appendix 5-8 are the key reports relating to this adverse event and the Data Verification plan.1

2.5. Sample size calculations for case-control studies

An iterative process was undertaken to achieve an estimate of the most appropriate sample size required to provide balance between adequate power to detect meaningful differences between cases and controls (for any given prevalence of a given exposure in the population) and feasibility of conducting the study. For example, to examine whether a characteristic which had an approximate prevalence of 10% among controls and an odds ratio of 2.25 when comparing the odds of exposure in cases and controls, a sample size of approximately 200 was required to have 80% power (with a 5% significance level and 1:1 case: control ratio). However, an odds ratio as high as 2.25 may not be present for many exposures and more subtle differences between cases and controls was allowed for. If an odds ratio of 1.7 was assumed instead (with 10% prevalence of an exposure among controls), then in order to achieve 80% power almost 600 cases and controls would be required. However, with the same odds ratio (OR: 1.7), same study power (80%) and prevalence of 20% among the controls instead, 300 cases and controls would be required.

Shown in the table below are assumptions for a sample size of 400 cases and 400 controls (approximately 30 cases and 30 controls per community, in the 14 communities of Arms A and B for Case-control study 1; and 60 cases and 60 controls per community in the 7 communities of Arm A for Case-control study 2). This sample size was appropriate to adequately balance power, importance (in relation to prevalence of an exposure among the controls) and feasibility.

[1] Due to the length of the reports these are inserted as hyperlinks which are available digitally only.

Table 2.1 Study power with sample size of 400 cases and controls for a range of exposure prevalence and odds ratio estimates

Prevalence of exposure in controls	Odds ratio for not accepting testing or starting treatment (depending on the study), comparing individuals with an exposure to those without	Power (%)
10%	1.75	71%
15%	1.75	85%
20%	1.75	91%
10%	2.0	90%
15%	2.0	97%
20%	2.0	99%

Assuming that the percentage of controls exposed to a particular risk factor was 10%, or 15%, or 20%, and that the odds ratio comparing exposed with unexposed individuals was 1.75, the corresponding study power to show an effect of the risk factor was 71%, 85%, and 91% respectively. With an odds ratio of 2, the corresponding figures for study power were 90%, 97%, and 99% respectively. When the proportion of controls exposed to a particular risk factor was 15% or more, the sample size was sufficient for stratified analyses, such as separate analyses by trial arm or country. When examining associations for men and women separately with 200 cases and 200 controls for each gender, if 15% and 20% of controls respectively were exposed to the risk factor, study power was 75% and 83% respectively, if the odds ratio comparing exposed with unexposed individuals was 2.

2.6. Data exploration and statistical analysis

2.6.1 Exploring the study population

The first step in understanding the study population was to explore the distribution of characteristics in the data-set – starting with the age, gender and other basic demographics and going on to tabulate all the variables to see the proportions in the study population with various characteristics. Variables were categorised as needed – based on what was logical e.g. grouping “strongly agree” with “agree” where numbers were too few to allow separate analysis or according to the

distribution of the data so that there were approximately equal proportions in each category. Note that the categories were created independently of case/control status.

This was followed by cross-tabulation of the variables (in above categories if relevant) with case/control status to provide understanding of the distribution of the variables by case/control status. The cross-tabulations were also performed stratified by country and by gender to add to understanding of the study population.

2.6.2 Logistic regression analysis

Stata 14 was used to perform logistic regression modelling to estimate odd ratios of the association between exposure variables and uptake of testing / TLA for CC1 and CC2, respectively. As the controls were frequency matched to cases by community and gender, all models included (and thus controlled for) community and gender. The estimated odds ratios adjusted for community and gender for each exposure of interest separately were examined (univariable analysis). Variables which were about demographic and behavioural characteristics were considered fundamental features which may have a confounding effect on associations with other variables and considered for addition to a multivariable model, while those which represented participant views or opinions were not. Variables which showed statistical evidence of association with case/control status on a Likelihood ratio test ($p \leq 0.05$) were examined to consider adding them to a multivariable logistic regression model. Age was added as an a-priori potential confounding factor.

Each variable (demographic or behavioural characteristic) which had statistical evidence of an association with case/control status was added along with age category, to the “crude” models (with community and gender included). A multivariable logistic regression model was then constructed, including all the variables (demographic or behavioural characteristics) with statistical evidence of association with case/control status (i.e. after adjustment for age, community and gender), to examine the adjusted odds ratios of each exposure variable in the study.

As mentioned above, Likelihood ratio testing (LRT) was done - comparing two models with and without a given exposure variable to examine the statistical evidence for association between the exposure variable and case/control status. A p-value of ≤ 0.05 was chosen as the threshold for evidence of association. Statistical evidence for effect medication of associations by gender and country were also explored using LRTs for variables which may have plausibly differed in association with the outcome, by gender or country, respectively. Models with interaction terms of a given exposure variable and gender or country as appropriate, were compared with models without interaction terms. A p-value of <0.05 was chosen as the threshold for evidence of interaction.

For variables with 3 or more response categories which had a possibility of a dose-response relationship, tests for trends were performed.

2.7. Safety monitoring and social harm reporting

2.7.1 Safety monitoring

Safety issues were not anticipated for these studies.

2.7.2 Social harm reporting

The HPTN defines social harms as any untoward social occurrence that happens to a participant as a result of their participation in the study, with examples including loss of employment, harassment by neighbours, shunned by family, rejection by partner, etc. Social harms were monitored during Case-control studies 1 and 2. Research assistants were trained to identify and report any direct negative social consequences of participation in the studies. If the study management team judged an individual social harm to be serious or unexpected, they would have worked together with appropriate bodies (in-country investigator, community advisory board, sponsor, IRB, etc.) to determine if a response was indicated, and if so, what it should have been.

2.8. Human subjects and ethical considerations

2.8.1 Risk-benefit assessment

As described above, only individuals who gave permission for approach by RAs had their information passed on to the RAs, by the CHiPs who obtained verbal assent for this. This information included the individual's name, gender, age and address - to facilitate approach of the client by a study RA. No information about HB-HTC acceptance/ non-acceptance or any details gathered during the CHiP intervention were conveyed for Case-control study 1. In Case-control study 2, no information about whether TLA was achieved by a given participant was given to RAs. We did however have to include the fact that the client was PLWH and was referred for TLA. Community members were explicitly informed of this by the CHiPs, when they asked for verbal permission.

Written informed consent was obtained by RAs before questionnaires were administered. The importance of confidentiality and sensitivity in administering the questionnaires were of highest priority in training and study preparation. All analyses were conducted after identifying information was removed from the data, and data were not traceable to individual participants. Provided these precautions were adhered to there were no major risks anticipated with participating in these studies.

The direct benefit from study participation were relatively minor, but consenting individuals did benefit from representing their communities and providing feedback about the PopART testing and

treatment intervention. There will be community-level benefits from the research – both to communities from which research participants originate and beyond. All research findings (aggregated and anonymised) will be shared with local and national health authorities to enhance understanding of barriers and facilitators of service uptake and where relevant to contribute towards improvements in service provision.

Participants were not paid or compensated for participation as there were concerns that it could bias the study sample or responses given. PopART leadership were also reluctant to set a precedent which required incentivisation for research participation.

2.8.2 Ethical review

The studies were approved by the relevant in-country and international ethical review boards (ethics committees of the University of Zambia, Stellenbosch University and the London School of Hygiene and Tropical Medicine), as part of the main PopART trial. The following study materials were submitted to the necessary ethics and regulatory authorities prior to study commencement:

i. Study Protocol Summary Document
ii. Verbal Permission Request Sheet (for use by CHiPs)
iii. Study Information and Informed Consent Form (for use by study RAs)

2.9 Funding

The funding for these studies is included in the main PopART / HPTN 071 trial budget[1] and no additional costs were incurred.

2.10 Timeline

The PopART trial commenced in some communities in Zambia in November 2013, but got underway in earnest in January 2014; while in South Africa some activities began in January and full roll-out in all communities was achieved in March 2014. After completion of the annual round, CC1 started in Zambia in February 2015 and in April in South Africa. CC2 commenced after an additional 6 months to allow for all those referred at the end of the annual round to link-to-care and initiate ART. In addition, as the same field RAs who were conducting CC1 were also responsible for CC2, the former study had to be completed before CC2 was able to finally start in October 2015. All CC study

[1] HPTN 071 is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) under Cooperative Agreements UM1-AI068619, UM1-AI068617, and UM1-AI068613, with funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Additional funding is provided through NIAID, the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the International Initiative for Impact Evaluation (3ie) with support from the Bill & Melinda Gates Foundation.

activities were completed by mid-2016 (including the additional activities involving data verification in South Africa related to the data fabrication issue).

Chapter 3: Home-based voluntary HIV testing in sub-Saharan Africa: a systematic review and meta-analysis

Outline of chapter

To contribute to the wider aim of the PhD to evaluate the factors associated with uptake of the key steps in the cascade of care provided by the PopART trial, a detailed understanding of the acceptability of HB-HTC was sought. A systematic review and meta-analysis of evidence was conducted. As this was carried out at the start of the PhD in 2012, the data examined were largely from the decade prior. At the time of writing this thesis document, more has been published on HB-HTC but conclusions about the acceptability of HB-HTC have not changed. As such, it was not considered productive for this systematic review to be updated. The study was published in PLoS Medicine and the manuscript is presented below.

Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N (2012) Uptake of Home-Based Voluntary HIV Testing in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. PLoS Med 9(12): e1001351. https://doi.org/10.1371/journal.pmed.1001351

3.1 Abstract

Introduction: Improving access to HIV testing is recognized as a key priority in scaling up HIV treatment and prevention services. Home-based testing (HBT) as an approach to delivering wide-scale HIV testing is explored in this study.

Methods and Findings: A systematic review and random effects meta-analysis of published studies reporting on uptake of HBT in sub-Saharan Africa since 2000 were conducted to assess the proportion of individuals accepting HBT and receiving their test result. Three electronic databases were searched.

Our initial search yielded 1199 articles, 114 were reviewed as full-text articles and 19 publications involving 21 studies (N=524,787 offered HBT) were included for final review. The studies came from 5 countries: Uganda, Malawi, Kenya, South Africa and Zambia.

The proportion of people who accepted HBT (N=474,516) ranged from 58.1% to 100%, with a pooled proportion of 83.8% (95%CI: 80.9-86.6%). Heterogeneity was high ($\tau^2$0.13). Sixteen studies reported on the number of people who received the result of HBT (N=432,835). The proportion of individuals receiving their results out of all those offered testing ranged from 24.9% to 99.7% with a pooled proportion of 77.4% (95%CI:74.0-80.7%), (τ^2 0.12). HIV prevalence ranged from 2.9%-36.5%. New diagnosis of HIV following HBT ranged from 40-79% of those testing positive. Forty-eight percent of those offered testing were men and they were just as likely to accept HBT as women (pooled odds ratio 0.84 (95%CI: 0.56-1.26) ($\tau^2$0.33). The proportion of individuals previously tested for HIV among those offered a test ranged from 5-66%.

No evidence was reported of negative consequences of HBT.

Conclusion: Home based voluntary counselling and testing has the potential to dramatically increase awareness of HIV status in previously undiagnosed men and women in sub-Saharan Africa. HBT is a gateway to accessing care early and the benefits for individual and public health, both for treatment and prevention, make it an invaluable tool in the fight against HIV.

3.2 Introduction

Testing for HIV is the first step in the cascade of care for HIV-positive individuals who need treatment. Knowledge of HIV status is also an important part of HIV prevention, for both HIV-negative and HIV-positive individuals, and innovative means to increase uptake of testing has recently been identified as an international policy priority (1-4). Despite some progress, knowledge of HIV status remains low in sub-Saharan Africa (SSA) where HIV prevalence is highest(5). National population surveys in six sub-Saharan African countries found that amongst participants living with HIV there was a wide range in respondents' awareness of their status (from 30% in Kenya to 70% in Congo)(5). Men were less aware of their status than women (in countries with available data)(5).

Home-based voluntary counselling and testing (HBT) has recently been suggested as an effective way to identify HIV-infected people earlier in the stage of their disease and so enrol people into care and treatment in a timely manner(6, 7). However, there is uncertainty about HBT and concern that it may be poorly accepted or even harmful, partly owing to the enduring climate of stigma and discrimination around HIV/AIDS in many settings (8, 9).

We carried out a systematic review and meta-analysis of the available evidence for acceptability of HBT in SSA, and assessed a number of potential determinants of uptake and programme success.

3.3 Methods

We conducted this systematic review and meta-analysis according to the criteria set out by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group(10) and devised a pre-defined search protocol. The specific objectives of the study were to summarise the following proportions: "accepted" (or uptake), defined as accepted and had HIV test performed at home as a proportion of all individuals offered HBT; "received", defined as obtained result of home-based HIV test as a proportion of all individuals who accepted; and "overall" defined as the proportion of patients who received a test result among all those offered VCT (including refusals). We also planned sub-group analyses as outlined below.

Search strategy

We aimed to summarize studies that described uptake of HIV testing provided at home in SSA. We screened studies published between January 2000 (the onset of programmes providing antiretroviral therapy in SSA) and 31st March 2012. The following study designs were permitted: randomised controlled trials, observational cohort studies, cross-sectional surveys, and programme evaluations. Any study that described an intervention to provide HIV testing at home and reported proportions

accepting HIV testing out of all individuals offered a home based HIV test was included. Where acceptance of testing was reported, it was assumed that testing was performed unless stated otherwise.

To avoid duplication we excluded reports that pooled data from previously published studies, and where there was substantial overlap of study subjects we included the study with the most complete information. No language or age restriction was applied. To identify studies for this systematic review we searched Pubmed, Embase and Global Health electronic databases and manually searched the bibliographies of relevant articles. We only included peer-reviewed journal articles; conference abstracts were excluded. Anticipating overlap between studies reporting HBT and other community-based strategies, we developed a broad compound search strategy that combined terms for "HIV" and "voluntary counselling and testing"; "home based", "mobile", "community", "workplace", "couples" and "self". We then combined these terms with individual names of countries in SSA (Supporting Information 3.1). Finally, we excluded all studies that did not report home-based delivery of HIV testing.

Eligibility of abstracts and journal articles was determined by one investigator (KS) and verified by a second researcher (RVdB). Two investigators (KS, RVdB) then independently extracted data on study characteristics and outcomes using a standardised form. Any disagreements regarding eligibility or outcome data were verified by a third investigator (NF). The rigour of study processes and research methods was examined using pre-defined criteria but studies were not excluded for quality reasons.

Data synthesis and analysis

We calculated the proportion of people who accepted HIV testing at home and the proportion who received their test result, out of those i) who were offered and ii) who accepted testing. The variance of raw proportions was stabilised using a Freeman-Tukey type arcsine square-root transformation and proportions were then pooled using a DerSimonian-Laird random-effects model (11-13). Pooled odds ratios were calculated for proportions stratified by gender using the same method. We report the I2 statistic to assess the proportion of variability due to between-study heterogeneity (but this estimate is known to increase as the number of subjects contributing to the meta-analysis increases(13)). We therefore also report $\tau 2$ as a measure of between-study variance (reported on the arcsine square-root scale). We explored potential sources of heterogeneity through univariate subgroup analysis to determine the potential influence of the following covariates: HIV prevalence (<10% vs ≥10%), study period (<2005 vs ≥2005), incentives provided, sensitization campaigns done, and study setting (urban vs rural). We further explored the potential influence of type of test (point-of-care testing with immediate result and whether oral specimens were used). Finally, subgroup

analyses were done to assess the potential influence of the proportion of individuals in the study who had previously tested (arbitrarily divided into 2 categories, <30% vs ≥30%), and targeted HBT of household members of index HIV-positive individuals. All analyses were conducted using Stata version 12.0 (Stata Corp, College station, Texas).

3.4 Results

Characteristics of included studies

Our initial search yielded 1199 articles, of which 114 were reviewed as full-text articles and 19 were included in the final review (Figure 3.1) after excluding four studies with clearly overlapping study populations(14-17). Two publications presented data of 2 sub-studies: the first article included data from two surveys done in two separate time periods(18); the second article reported different sub-sets of individuals (residents and migrants)(19). As such, we present data and results of analyses based on these 21 studies from the 19 articles. The studies were from 5 countries: Uganda(20-27), Malawi(18, 28-31), Kenya(32, 33), South Africa(19, 34) and Zambia(35), and carried out between 1999 and 2010. Most studies focused on adults (defined variously as aged ≥18years or, more commonly ≥15years) while 7 studies also included children(20, 22, 24, 25, 27, 32, 34). Regional HIV prevalence (reported by the authors for the study areas or obtained from UNAIDS contemporaneous national data) ranged from 4.4-22% (Table-1).

Testing was generally provided by counsellors; one study included laboratory assistants in the testing teams (24) and two utilised nurses (23,34). One study employed self-testing with counsellor supervision(28). HIV prevalence amongst those tested ranged from 2.9% to 36.5%. One study reported giving advice for repeat testing after 3 months to people testing HIV negative(18). Two other studies reported HIV prevention counselling for negative individuals (23,32). Ten studies reported some means of linkage to care, mostly advising HIV-positive patients to seek care at the nearest health facility(18, 20, 22-24, 28, 31-33, 36). One study presented data on the proportion of individuals linked into care upon testing HIV-positive, with 97 %(N=11,033) initiated on co-trimoxazole prophylaxis (24). Two studies presented information on the clinical condition of individuals found to be HIV-positive (22,24). Following HBT a higher proportion of HIV-positive individuals had CD4 counts above treatment initiation thresholds (>200 cells/mm3) than below (22,24).

Table-2 summarises the factors that potentially influence the rigour of the studies and shows that there was wide variation in standards of implementation and research.

Proportion of individuals accepting testing and receiving results

A total of 524,787 people were offered HBT across the 21 studies which ranged in size from 216(28) to 282,857(24) people. Twelve studies disaggregated data by gender with 180,942 men and 198,042 women, offered testing overall (19-25,28-3035). The proportion of men who were offered testing (in the studies which reported on gender) ranged from 26% to 49%, with an overall proportion of 48%.

Across all 21 studies the proportion of people who accepted HBT ranged from 58.1%(95%CI:57.5-58.8%) to 100%(95%CI:100-100%) , with a pooled proportion of 83.8%(95%CI:80.9 -86.6%) accepting to be tested (N=474,516) (Figure 3.2). Heterogeneity was high (τ20.13). Overall, men were just as likely as women to accept testing: 78.5% (95%CI 78.3-78.7%) of men (N=140,459) and 82.4% (95%CI 82.3-82.5%) of women (N=163,238). The pooled odds ratio of men accepting HBT was 0.84 (95%CI: 0.56–1.26%) that of women (τ2 0.33). Studies which offered targeted HBT to household members of index HIV-positive individuals achieved higher proportions of acceptance than the other studies: 96.0% (95%CI:92.2-99.8%) vs 81.7% (95%CI:77.9-85.4%) (p<0.001).

Sixteen studies reported on the number of people who received the result of HBT (N=432,835)(18, 20-24, 26-30, 32, 33, 35, 36). The proportion receiving a result out of those who accepted testing ranged from 36.8% (95%CI:33.9-39.7%) (26) to 100% (95%CI:100-100%) (32) with a pooled proportion of 99.1% (95%CI:98.9-99.1%) receiving their result (τ2 0.12) (Supplementary Figure 3.1). The proportion of individuals receiving their results overall (out of all those offered testing) ranged from 24.9% (95%CI: 22.8-27.1%) to 99.7% (95%CI: 99.7-99.8%) with a pooled proportion of 77.4% (95%CI: 74.0-80.7%) (τ2 0.12) (Figure 3.3).

Eleven studies (N=456,283) reported on the number of individuals offered testing who had already been previously tested (N=78,527)(18, 21-25, 28-30, 32, 36); 3 studies reported on the number tested within the last 12 months(18, 23, 26). However, authors did not report the definition of 'previously tested' and whether it included all those who had had a test or was limited to those who received their result and became aware of their HIV status. The proportion of individuals previously tested ranged from 5-66% overall (11 studies); 22-50% were previously tested within the last 12 months (3 studies). Studies in which <30% of people had previously been tested (5 studies, N=436,618) (22, 24, 25, 29, 32) were more likely to report a higher frequency of test acceptance compared to studies in which ≥30% of people had been previously tested (6 studies, N=19665)(18, 21, 23, 28, 30, 36) (92.1%(95%CI:87.6-96.7%) vs 83.8%(95% CI 77.7-89.9%), p=0.03).

One study (Kimaiyo et al) explicitly reported excluding individuals already known to be HIV-positive (32). Angotti et al reported that 68%(11/72) of known HIV-positive individuals accepted HBT vs

90%(1430/1588) amongst individuals who were HIV-negative when they previously tested(18). Choko et al invited participants to partake in oral self-testing even if they knew they were HIV-positive(28) (19/175 who had previously tested). Amongst individuals previously tested for HIV who accepted HBT in the study by Matovu et al 10% (N=350/3362) were already known to be sero-positive. Of those testing HIV-positive through HBT, 40-79% had not previously been diagnosed (5 studies)(14, 23, 25, 28, 32) (the information for the study by Matovu et al was obtained from a second publication in 2005(14)).

Supplementary Table-1 summarises the individual level factors associated with uptake of testing and shows a wide variation in findings across the studies which reported on this(20, 21, 23, 24, 29, 30).

Potential harm and cost considerations

Eight of the articles we examined acknowledged the potential for harm from testing for HIV(20, 22, 24, 26, 27, 30, 33, 34) and none reported any. Four of these described no adverse events and suggested that HBT could serve to normalise HIV testing by its uniform and non-discriminatory deployment regardless of risk factors or health status(20, 22, 24, 26). Wolff et al presented qualitative research findings that fear of stigmatisation and emotional vulnerability associated with receiving results from public facilities were the most common explanations for the relative popularity of HBT(26). A further three articles noted that concerns about stigma and fears about confidentiality could account for non-participation in HBT (30,3334); uptake in these studies was 71-98%. Another study commented that confidentiality may be enhanced with HBT(27). Two studies (both from Uganda) reported on the costs of HBT and demonstrated that the cost of testing per client was less than $9USD (22,24).

Heterogeneity

Statistical heterogeneity as measured by I2 was high. However, over three quarters of the studies (16/21 studies; N=483,472) reported an acceptance rate above 75%. Subgroup analyses to examine heterogeneity did not find any differences in HBT uptake and receipt of results according to study period, study setting, or whether or not sensitization campaigns were reported as being done (Figure 3.4). The provision of incentives appeared to result in higher test uptake and immediate provision of results increased the frequency of receiving the test result. Studies in which <30% of individuals had been previously tested or those in sites where local HIV prevalence was <10% also had higher uptake of testing (Figure 3.4).There was also a tendency towards a greater frequency of test acceptance when immediate provision of results was available (87.6% (95%CI: 83.8-91.3%) vs 79.2% (95%CI: 70.9-87.8%), p=0.07).

3.5 Discussion

This systematic review and meta-analysis of 19 papers based on 21 studies of HBT across 5 countries in SSA demonstrates that voluntary counselling and testing for HIV at home is highly acceptable with an average 84% of people accepting testing and 99% of those accepting testing receiving their result. Over three quarters of everyone who was offered a test accepted to be tested and received their result (77% in 16 studies reporting on this). The proportion of previously undiagnosed HIV was high (40-79% of those diagnosed HIV-positive), emphasising the value of HBT.

A study from Malawi of clinic based HIV counselling and testing showed that just 13.3% of 18,021 clinic attendances (8.5% amongst men) included HIV counselling and testing. This meta-analysis indicates that HBT is an important addition to other approaches such as stand-alone testing, community and work-place testing, as well as provider initiated testing that could dramatically improve awareness of HIV status in SSA.

Delayed presentation for HIV treatment services is recognised as an important cause of morbidity and mortality from HIV despite major progress in increasing access to antiretrovirals (37). Both studies which reported on clinical status of patients diagnosed HIV-positive upon HBT, found that a higher proportion of them had CD4 counts above treatment initiation thresholds (for the study period) than below this threshold. This has implications for earlier treatment and better prognosis (7,38), as well as higher impact for treatment as prevention endeavours (39,40). A recent pilot study in South Africa found a reduction in mean community viral load six months after the introduction of a HBT campaign(41).

While women are disproportionately affected by HIV in SSA(5), men have long been known to under-utilise HIV services and present later for care than women, and consequently have worse outcomes on treatment(42-44). In the studies reviewed here, an overall proportion of 48% of those offered testing were men. This compares favourably with facility-based testing where testing of males attending the clinic may be as low as 9%(44). In our meta-analysis of HBT men were just as likely as women to be offered a test, and to accept testing, giving promise to greatly improving awareness of HIV status for both sexes. Studies which provided results at a distant site even if testing was conducted at home were associated with lower proportions of people receiving results out of those who accepted testing, emphasising the benefits of HBT including immediate result provision in raising awareness of HIV status.

While the results of subgroup analyses need to be interpreted with caution, they suggest that the running of pre-test sensitization campaigns may be of little benefit in terms of uptake of HBT.

However, these are essentially “ecological” comparisons which may be confounded by many other differences between the study populations examined. Also, the number of studies where incentives were given was very small (Table 1), and strong conclusions cannot be drawn. Nevertheless, the fact that most of the studies demonstrated similar proportions of uptake of HBT perhaps argues against a strong effect. The finding that studies with a lower proportion of individuals previously tested for HIV (<30%) had a higher frequency of test uptake points to the value of HBT as an effective approach to engage those not previously aware of their HIV status in testing. Targeted HBT of index HIV-positive clients’ household members may be an effective way to achieve higher acceptance in settings where more general HBT is not feasible.

Uptake of HBT may be influenced by availability of treatment, as indicated by the fact that the study with the lowest overall success (only 25% of people offered a test received their result) was done at a time when antiretroviral treatment was not available in the communities studied(26) (although overall there was no effect of “study period”). However, there may be other confounding factors involved and this study was based on a small sample size; in sensitivity analysis, excluding it from the analysis did not change the overall result (data not shown). Three other studies were notable for having <70% receipt of results amongst those who accepted HBT (Supplementary Figure 3.1). Two of these studies did not provide immediate result after testing (18,21), while the third (20) offered the option of receiving results later.

Human rights protections should be an integral part of any testing campaign and every effort should be made to avoid physical, social and psychological harm to individuals (8,9). However, the high level of uptake we have found overall seems to indicate acceptability of HBT in the communities studied.

There are several strengths and limitations to this review. We used a broad search strategy that allowed us to capture a relatively large number of studies, resulting in a large overall sample size and giving increased confidence in the pooled estimates. There was high statistical heterogeneity, as expected for pooled proportions in observational studies. We limited our search to studies conducted in SSA over the last decade in order to improve comparability, and used a random-effects model to pool data. We undertook a number of sensitivity and subgroup analyses to explore potential sources of heterogeneity. Another limitation was that, as a trade-off to using a broad search strategy, our search was limited to just 3 databases, and published articles in peer-reviewed journals. We therefore cannot rule out the possibility that we may have missed some studies, or the possibility of publication bias leading to the non-publication of studies with lower uptake.

Our findings indicate a number of directions for future research. In particular, the suggestion that the conduct of sensitization campaigns have little or no impact on uptake of HBT and receipt of results has important implications for programme cost and efficiency, and deserves further evaluation. Other key areas for further research include linkage to care following HBT and repeated HBT for ongoing knowledge of HIV status. Sustainability and cost considerations (short and long-term) are important to help guide policy and further work on cost-effectiveness is required.

In conclusion, home based voluntary counselling and testing has the potential to dramatically increase awareness of HIV status in previously undiagnosed men and women in sub-Saharan Africa. HBT is a gateway to accessing care early and the benefits for individual and public health, both for treatment and prevention, make it an invaluable tool in the fight against HIV.

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3.6 References

1. World Health Organization. WHO Consultation - The Strategic Use of Antiretrovirals for Treatment and Prevention of HIV Geneva, Switzerland, 14-16 November 2011.Executive Summary. http://wwwwhoint/hiv/pub/meetingreports/consultation_20111116pdf. 2011.
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Getting to zero: 2011-2015 strategy Joint United Nations Programme on HIV/AIDS. http://wwwunaidsorg/en/media/unaids/contentassets/documents/unaidspublication/2010/jc2034_unaids_strategy_enpdf. 2010.

3. De Cock KM, Bunnell R, Mermin J. Unfinished business--expanding HIV testing in developing countries. The New England journal of medicine. 2006; **354**(5): 440-2.

4. Walensky RP, Bassett IV. HIV self-testing and the missing linkage. PLoS Med. 2011; **8**(10): e1001101.

5. World Health Organization. Global HIV/AIDS Response. Epidemic update and health sector progress towards Universal Access, Progress Report. http://whqlibdocwhoint/publications/2011/9789241502986_engpdf. 2011.

6. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS World AIDS Day Report. http://wwwunaidsorg/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_enpdf. 2011.

7. Wachira J, Kimaiyo S, Ndege S, Mamlin J, Braitstein P. What is the impact of home-based HIV counseling and testing on the clinical status of newly enrolled adults in a large HIV care program in Western Kenya? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012; **54**(2): 275-81.

8. Turan JM, Bukusi EA, Onono M, Holzemer WL, Miller S, Cohen CR. HIV/AIDS stigma and refusal of HIV testing among pregnant women in rural Kenya: results from the MAMAS Study. AIDS and behavior. 2011; **15**(6): 1111-20.

9. Human Rights Watch. A testing challenge: the experience of Lesotho's universal HIV counseling and testing campaign. http://wwwhrworg/sites/default/files/reports/lesotho1108pdf. 2008.

10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA : the journal of the American Medical Association. 2000; **283**(15): 2008-12.

11. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-analysis. Wiley, Chichester; 2009.

12. Freeman M. Transformations related to the angular and the square root. Annals of the Institute of Statistical Mathematics. 1950; **21**: 607-11.

13. Rucker G, Schwarzer G, Carpenter J, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 2008; **8**: 79.

14. Matovu JK, Gray RH, Makumbi F, Wawer MJ, Serwadda D, Kigozi G, et al. Voluntary HIV counseling and testing acceptance, sexual risk behavior and HIV incidence in Rakai, Uganda. AIDS. 2005; **19**(5): 503-11.

15. Mutale W, Michelo C, Jurgensen M, Fylkesnes K. Home-based voluntary HIV counselling and testing found highly acceptable and to reduce inequalities. BMC Public Health. 2010; **10**: 347.

16. Obare F, Fleming P, Anglewicz P, Thornton R, Martinson F, Kapatuka A, et al. Acceptance of repeat population-based voluntary counselling and testing for HIV in rural Malawi. Sex Transm Infect. 2009; **85**(2): 139-44.

17. Vreeman RC, Nyandiko WM, Braitstein P, Were MC, Ayaya SO, Ndege SK, et al. Acceptance of HIV testing for children ages 18 months to 13 years identified through voluntary, home-based HIV counseling and testing in western Kenya. J Acquir Immune Defic Syndr. 2010; **55**(2): e3-10.

18. Angotti N, Bula A, Gaydosh L, Kimchi EZ, Thornton RL, Yeatman SE. Increasing the acceptability of HIV counseling and testing with three C's: convenience, confidentiality and credibility. Soc Sci Med. 2009; **68**(12): 2263-70.

19. Welz T, Hosegood V, Jaffar S, Batzing-Feigenbaum J, Herbst K, Newell ML. Continued very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. AIDS. 2007; **21**(11): 1467-72.

20. Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, et al. Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial. J Acquir Immune Defic Syndr. 2010; **55**(2): 245-52.

21. Matovu JK, Kigozi G, Nalugoda F, Wabwire-Mangen F, Gray RH. The Rakai Project counselling programme experience. Trop Med Int Health. 2002; **7**(12): 1064-7.

22. Menzies N, Abang B, Wanyenze R, Nuwaha F, Mugisha B, Coutinho A, et al. The costs and effectiveness of four HIV counseling and testing strategies in Uganda. AIDS. 2009; **23**(3): 395-401.

23. Sekandi JN, Sempeera H, List J, Mugerwa MA, Asiimwe S, Yin X, et al. High acceptance of home-based HIV counseling and testing in an urban community setting in Uganda. BMC Public Health. 2011; **11**: 730.

24. Tumwesigye E, Wana G, Kasasa S, Muganzi E, Nuwaha F. High uptake of home-based, district-wide, HIV counseling and testing in Uganda. AIDS Patient Care STDS. 2010; **24**(11): 735-41.

25. Were WA, Mermin JH, Wamai N, Awor AC, Bechange S, Moss S, et al. Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda. J Acquir Immune Defic Syndr. 2006; **43**(1): 91-5.

26. Wolff B, Nyanzi B, Katongole G, Ssesanga D, Ruberantwari A, Whitworth J. Evaluation of a home-based voluntary counselling and testing intervention in rural Uganda. Health Policy Plan. 2005; **20**(2): 109-16.

27. Were W, Mermin J, Bunnell R, Ekwaru JP, Kaharuza F. Home-based model for HIV voluntary counselling and testing. Lancet. 2003; **361**(9368): 1569.

28. Choko AT, Desmond N, Webb EL, Chavula K, Napierala-Mavedzenge S, Gaydos CA, et al. The Uptake and Accuracy of Oral Kits for HIV Self-Testing in High HIV Prevalence Setting: A Cross-Sectional Feasibility Study in Blantyre, Malawi. PLoS Med. 2011; **8**(10): e1001102.

29. Helleringer S, Kohler HP, Frimpong JA, Mkandawire J. Increasing uptake of HIV testing and counseling among the poorest in sub-Saharan countries through home-based service provision. J Acquir Immune Defic Syndr. 2009; **51**(2): 185-93.

30. Kranzer K, McGrath N, Saul J, Crampin AC, Jahn A, Malema S, et al. Individual, household and community factors associated with HIV test refusal in rural Malawi. Trop Med Int Health. 2008; **13**(11): 1341-50.

31. Molesworth AM, Ndhlovu R, Banda E, Saul J, Ngwira B, Glynn JR, et al. High Accuracy of Home-Based Community Rapid HIV Testing in Rural Malawi. J Acquir Immune Defic Syndr. 2010; **55**(5): 625-30.

32. Kimaiyo S, Were MC, Shen C, Ndege S, Braitstein P, Sidle J, et al. Home-based HIV counselling and testing in Western Kenya. East African Medical Journal. 2010; **87**(3): 100-8.

33. Negin J, Wariero J, Mutuo P, Jan S, Pronyk P. Feasibility, acceptability and cost of home-based HIV testing in rural Kenya. Trop Med Int Health. 2009; **14**(8): 849-55.

34. Shisana O, Stoker D, Simbayi LC, Orkin M, Bezuidenhout F, Jooste SE, et al. South African national household survey of HIV/AIDS prevalence, behavioural risks and mass media impact--detailed methodology and response rate results. S Afr Med J. 2004; **94**(4): 283-8.

35. Michelo C, Sandoy IF, Dzekedzeke K, Siziya S, Fylkesnes K. Steep HIV prevalence declines among young people in selected Zambian communities: population-based observations (1995-2003). BMC Public Health. 2006; **6**: 279.

36. Maheswaran H, Thulare H, Stanistreet D, Tanser F, Newell ML. Starting a home and mobile HIV testing service in a rural area of South Africa. J Acquir Immune Defic Syndr. 2012; **59**(3): e43-6.

37. May M, Boulle A, Phiri S, Messou E, Myer L, Wood R, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet. 2010; **376**(9739): 449-57.

38. Mills EJ, Ford N. Home-based HIV counseling and testing as a gateway to earlier initiation of antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012; **54**(2): 282-4.

39. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009; **373**(9657): 48-57.

40. Hayes R, Sabapathy K, Fidler S. Universal testing and treatment as an HIV prevention strategy: research questions and methods. Current HIV research. 2011; **9**(6): 429-45.

41. Barnabas R, Van Rooyen H, Baeten J, Tumwesigye E, Phakathi Z, Tumwebaze H, et al. Significant decrease in community viral load six months after a program of home-based HIV counseling and testing and facilitated referral to HIV care in KwaZulu-Natal, South Africa. Treatment as Prevention Vancouver Workshop, Canada 2012; **Oral presentation**.

42. Braitstein P, Boulle A, Nash D, Brinkhof MW, Dabis F, Laurent C, et al. Gender and the use of antiretroviral treatment in resource-constrained settings: findings from a multicenter collaboration. J Womens Health (Larchmt). 2008; **17**(1): 47-55.

43. Ochieng-Ooko V, Ochieng D, Sidle JE, Holdsworth M, Wools-Kaloustian K, Siika AM, et al. Influence of gender on loss to follow-up in a large HIV treatment programme in western Kenya. Bulletin of the World Health Organization. 2010; **88**(9): 681-8.

44. Macpherson P, Lalloo DG, Choko AT, Mann GH, Squire SB, Mwale D, et al. Suboptimal patterns of provider initiated HIV testing and counselling, antiretroviral therapy eligibility assessment and referral in primary health clinic attendees in Blantyre, Malawi*. Trop Med Int Health. 2012.

Table 3.1: Characteristics of included studies

Author, Publication Year	Country, setting	Period of study	N offered testing	Purpose of study	HIV prevalence[a]	Age eligibity of participants	Testing provider	Community sensitization described	Incentives provided	Sampling method and tests used	Previously tested %
Angotti (1), 2009	Malawi, 3 rural districts	2004	3659	Longitudinal HIV prevalence study	4.4-7.9%	15-49y	Locally trained VCT counselors	Yes	No	Oral swab (Orasure)(2004)	Not specified
Angotti (2), 2009	As above	2006	3459	As above	As above	As above	As above	As above	As above	FP RDTs[b] (Determine & UniGold) (2006)	66%
Choko, 2011	Malawi, urban district	2010	216	Feasibility of (supervised) oral self testing	*11%*	22-32y	Self administered (supervision from VCT counselor)	No	No	Oral swab (Oraquick) followed by FP RDTs (Determine and UniGold)	63%
Helleringer, 2009	Malawi, rural district	2006	751	Uptake of HBT	*11%*	18-35y	Trained health counsellors	Yes	Yes Bar of soap	FP RDTs (Determine and UniGold)	21%
Kimaiyo, 2010	Kenya, 2 rural districts	2007-9	101167	Feasibility and acceptability of HBT	*6.3%*	>13y and eligible children[c]	Counsellors trained for purpose	Yes	No	FP RDTs (Determine and Bioline)	26%[d]
Kranzer, 2008	Malawi, rural district	2005-6	2047	Factors associated with HBT refusal	11.4%	18-59y	Trained local VCT counselors	No	No	Venous blood sampling for ELISA[e] & particle agglutination testing in laboratory	36%
Lugada, 2010	Uganda, 5 rural districts	2005-7	4798	Uptake of HBT vs clinic based testing in household members of HIV-positive index patient	5.6%	Any	Trained lay field workers	No	No	FP RDTs (Determine screening, Unigold confirmation)	Not specified

Maheswaran, 2012	South Africa, rural district	2009	1726	Uptake of HBT and community mobile HIV testing and factors associated with HBT vs mobile testing	22%	≥15y	HIV Counsellors	No	No	Not specified[f]	40%
Matovu, 2002	Uganda, rural district	1999-2000	11709	Uptake of HBT and effects on sexual risk behavior and HIV acquisition	*5.6%*	15-49y	Counsellors	No	No	Venous blood sampling for ELISA(^{x2}) testing in laboratory	55%
Menzies, 2009	Uganda, setting not specified	2003-5	49470	Comparison of 4 testing approaches: door-to-door HBT, household member HBT (of index patient) – please clarify wording for this one, stand alone, hospital based VCT	*5.6%*	Any	Not specified	Yes	No	FP RDTs (screening test followed by confirmation if HIV-positive; tests not specified)	10%
Michelo, 2006	Zambia, one rural, one urban district	2003	5445	HIV prevalence survey	*20.4%*	15-59y	Not specified	No	No	Bionor saliva test + "serum test" for saliva positive or second saliva test	Not specified
Molesworth, 2010	Malawi, rural district	2007-8	16894	To assess the performance of HIV RDTs in a HIV prevalence survey	11.6%	≥15y	Non-laboratory basic health personnel	Yes	No	Venous blood sampling for RDTs (Determine & Unigold in parallel pre-May 2008, serially post -May 2008)	Not specified
Negin, 2009	Kenya, rural province	2008	2033	Feasibility, acceptability and cost of HBT	7.8%	15-49y	Lay counsellors	Yes	No	FP RDTs (Determine and Bioline)	Not specified

Sekandi[g], 2011	Uganda, urban district	2009	508	Uptake of HBT and factors associated with HBT	*6.5%*	≥15y	Trained nurse counsellors	No	No	FP RDTs (Determine screening, Statpak confirmation)	61%
Shisana, 2004	South Africa, nationwide	2002	9963	HIV prevalence survey	*26.5%*	≥2y	Nurses	No	Yes Money provided to head of household	FP onto filter paper; ELISA (x2) testing in laboratory	Not specified
Tumwesigye, 2010	Uganda, rural district	2004-7	282857	Acceptability and uptake of HBT	*5.4%*	>14y & eligible[h] children >18m	Counsellor and laboratory assistant teams	Yes	Yes HIV-positive provided with condoms, insecticide treated bednets & home water treatment equipment	FP RDTs (Determine screening, Statpak confirmation)	9%
Welz (1), 2007	South Africa, rural district	2003-4	19867	HIV prevalence survey (residents)	*27.9%*	Women 15-49y Men 15-54y	Trained fieldworkers	No	No	FP onto filter paper; ELISA (x2) testing in laboratory	Not specified
Welz (2), 2007	As above	As above	916	HIV prevalence survey (subset of migrants in the community)	As above	As above	As above	No	No	As above	Not specified
Were, 2003	Uganda, rural district	Not specified	2373	Uptake of VCT HBT	*4.1%*	Any	Not specified	No	No	Venous sampling, tests not specified	Not specified
Were, 2006	Uganda, 2 rural	2003-4	3338	Acceptability of HBT and HIV prevalence among household members of HIV-positive index patient	*4.1%*	Any	Counsellors	No	No	FP onto filter paper; ELISA (x2) testing in laboratory; For children <24m - HIV DNA measurement on dried blood spot	4.9%

Wolff[i], 2005	Uganda, rural (15 villages)	2001	1591	Uptake of HIV results from HIV prevalence survey	*7.9%*	≥15y	Counsellors	No	No	Venous blood sampling for ELISA (x2) testing in laboratory	Not specified

[a] data from study area or UNAIDS national data (adult prevalence) if shown in italics [b] FP RDT = finger prick rapid diagnostic test [c] eligible if <13y and mother HIV +ve, mother unknown HIV +ve living status, mother dead [d] 35,815/137,268 encountered in the area [e] Emzyme Immunosorbent Assays [f] Stated only as following national guidelines for testing [g] Excluded non-English and non-Lugandan speakers [h] eligible if mother deceased or HIV-positive [i] study done in period before antiretrovirals were available

Table 3.2: Assessment of Study Rigour

	Study Process Quality Indicators									Research Method Quality Indicators	
Author, Publication Year	**Pre-test counseling done[a]**	**Consent provided**	**Test offered based on giving results**	**Confirmatory laboratory testing done**	**Discordant results addressed[a]**	**Repeat sampling if discordant**	**Repeat visits if absenteeism**	**Specific advice if HIV result negative**	**Linkage to care for HIV infected**	**Sampling strategy described**	**Selective outcome reporting**
Angotti, 2009	Yes	Yes	Yes	No	Not specified	No	No	Yes, retest in 3 months time	Yes	Yes	No
Choko, 2011	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No
Helleringer, 2009	Yes	Yes	No	No	Not specified	Yes	Yes	No	No	Yes	No
Kimaiyo, 2010	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes, behaviour change &"ABC's" of HIV prevention	Yes	No	No
Kranzer, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Lugada, 2010	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Maheswaran, 2012	Yes	Yes	Yes	No	Not specified	No	No	No	Yes	No	No
Matovu, 2002	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No
Menzies, 2009	Yes	Yes	Yes	Yes	Not specified	Yes	No	No	Yes	No	No
Michelo, 2006	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Molesworth, 2010	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
Negin, 2009	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No
Sekandi, 2011	Yes	Yes	Yes	No	Yes	Yes	No	Yes, HIV prevention counseling	Yes	Yes	No
Shisana, 2004	Not specified	Yes	No	Yes	Not specified	Yes	Yes	No	No	Yes	No
Tumwesigye,	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No

2010											
Welz, 2007	Not specified	Yes	Yes	Yes	Not specified	Yes	Yes	No	No	Yes	No
Were, 2003	Yes	Yes	No	No	Not specified	No	Yes	No	No	No	No
Were, 2006	Not specified	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Wolff, 2005	Not specified	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No

[a] Where no information is available – 'not specified' is indicated for these variables as we considered it possible that these activities were done but not reported in the paper [b] Some studies offered testing and results were not promised eg. available only if client sought the result separately or entirely blinded testing was done for anonymous population HIV prevalence estimation

Figure 3.1: Flow diagram of study selection process

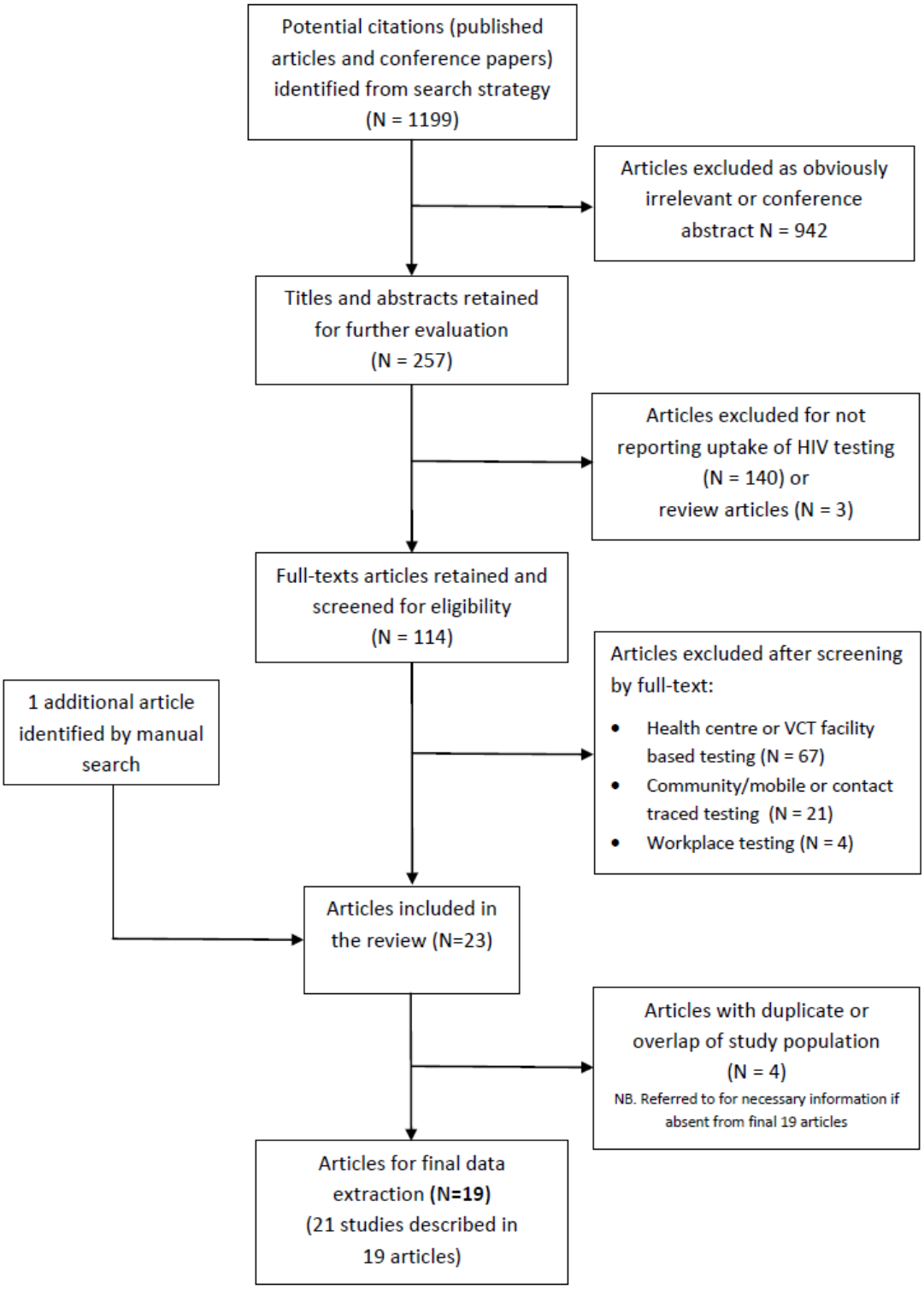
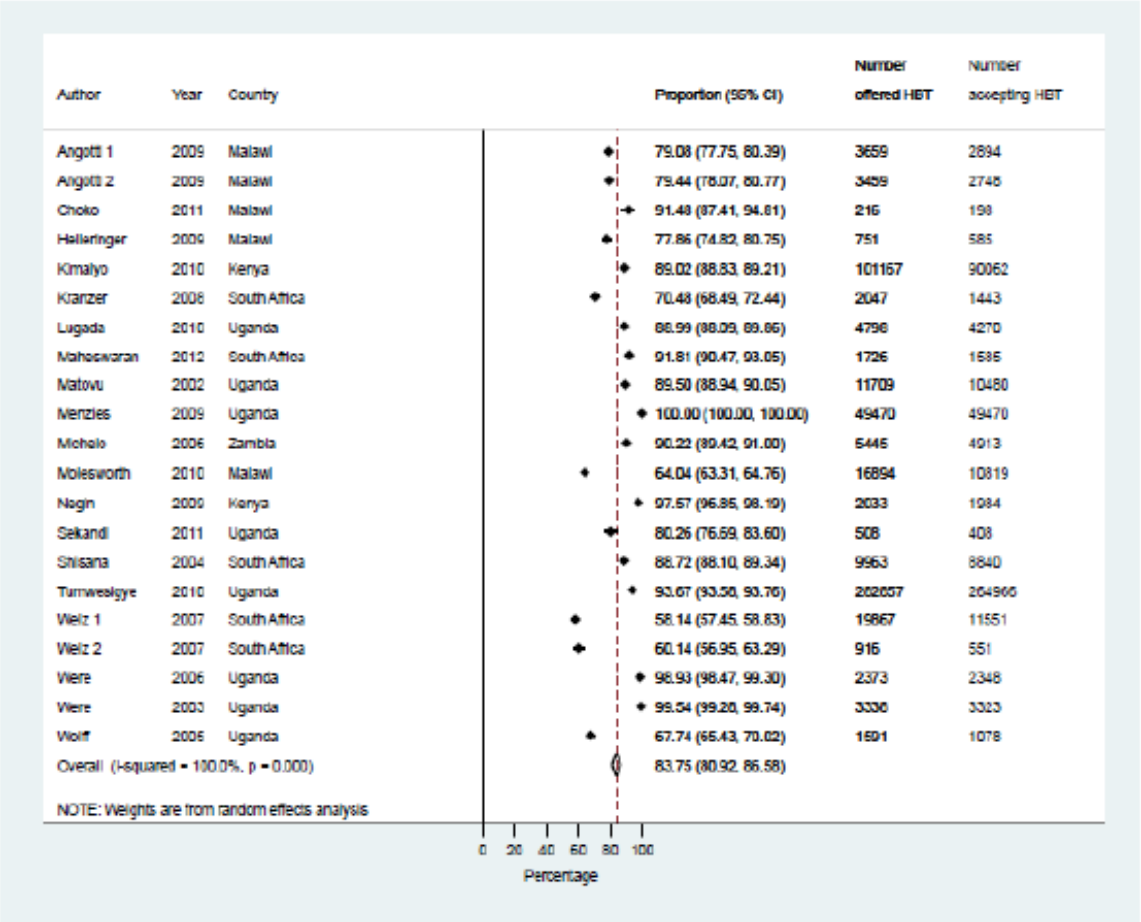
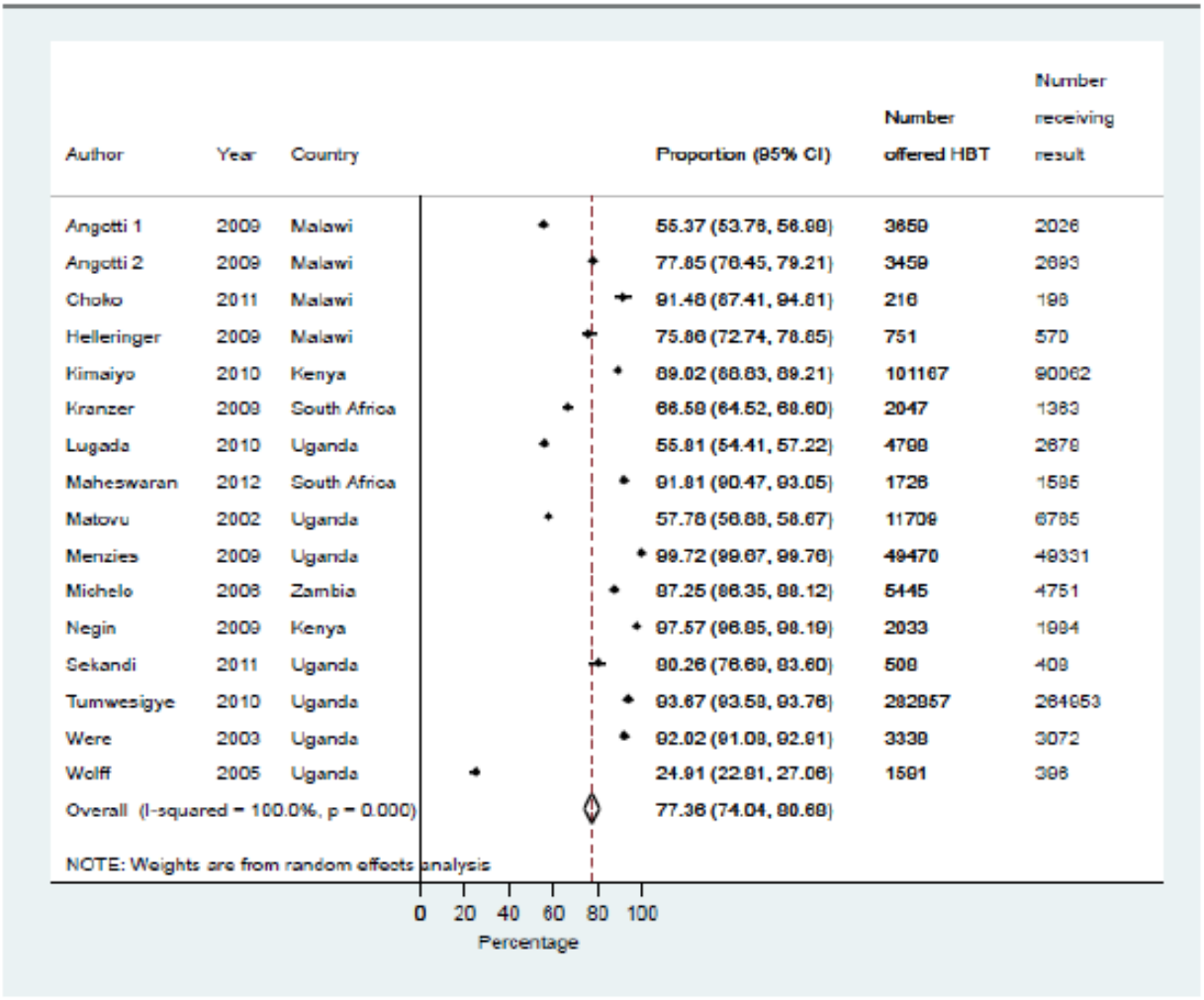


Figure 3.2: Proportion accepting HBT



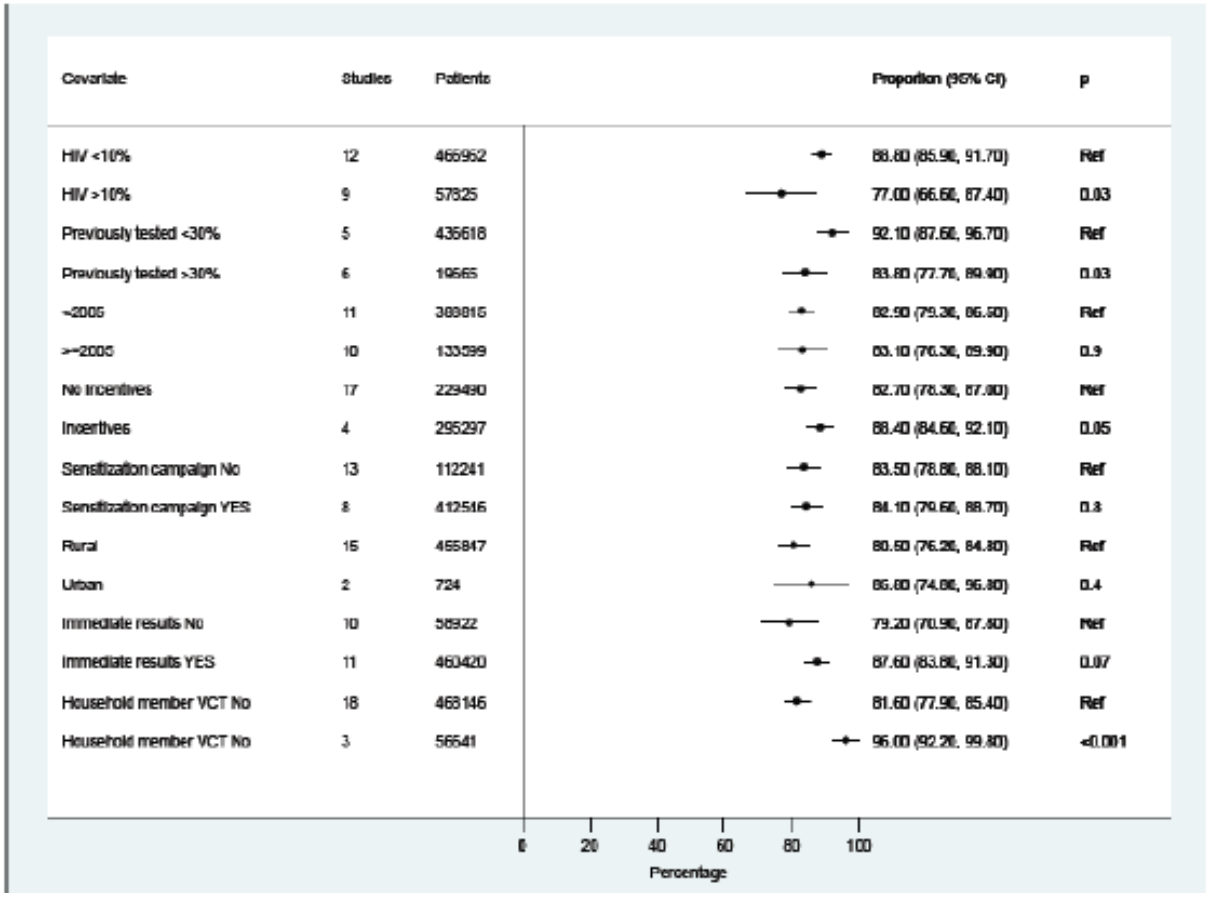
NB: "Accepted" - accepted and had HIV test performed at home as a proportion of all individuals offered ("offered" - presented opportunity to have HIV test performed at home)

Figure 3.3: Proportion achieving knowledge of HIV status overall



NB:"Overall" – the proportion of individuals who received a test result among all those offered VCT (including refusals).

Figure 3.4: Subgroup analyses

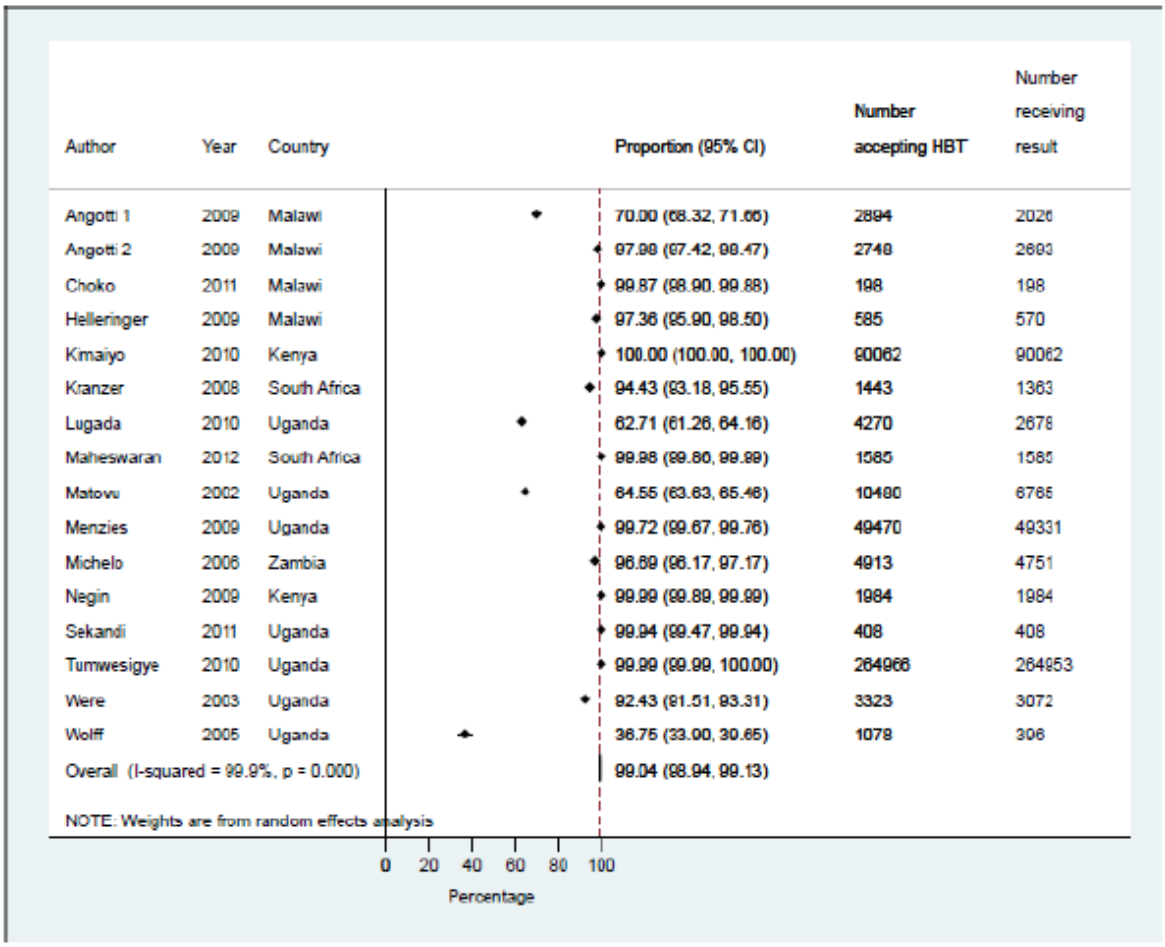


Supplementary Table 3.1: **Studies reporting predictors of uptake of HBT**

Author, Publication year	Positive association with HBT uptake	Negative association with HBT uptake	No statistically significant association (aOR)	Comments
Helleringer, 2009	Income bottom quartile; Symptomatic STI in last 3m	Age>25y; Having concurrent partnership at time of HBT	Gender; Marital status; Schooling; Religion; Residence mainland; No. of sexual partners past 3y; Ever tested prior to study	
Kranzer, 2008[a]	Female (Odds Ratio not given); Never married; Farmer profession; Older (>45y) head of HH[b]; >7% HIV prevalence in cluster	Female counsellors approaching male clients; Wife of head of HH[b] man who's not tested OR Wife of head of HH[b] man who's not part of study OR head of HH[b] is non-husband; <1km from main road	Age	Men less likely to be found at home
Lugada, 2010	Female; Age: <14 or >35y when compared with 15-24	Index HIV-positive client CD4 >200 (compared to <50)	Index client education level; No. of persons in HH [b]	
Matovu, 2002	Currently married or Divorced/widowed/separated compared to never married	Primary/post primary education compared to no education; Prior self-reported VCT or no prior VCT compared to prior VCT in the programme; HIV +ve vs HIV-ve; Condom use vs no condom use in past 6m	Age; Gender; Self-perception of HIV risk; No. of sexual partners	
Sekandi, 2011	Male; Age ≥35y compared to 15-24y; Previously married; Previous HIV testing in last 12m	Not Applicable	Age 25-34y: Religion; Education level; Previous HIV testing > 12m prior	
Tumwesigye, 2010	Female	Not Applicable	Not Applicable	Females more likely to be found at home

[a] Study actually reports refusal of HBT [b] Household

Supplementary Figure 3.1: Proportion receiving result of HBT



NB:"Received" - obtained result of home-based HIV test as a proportion of all individuals who accepted

Supporting Information 3.1: Search terms and Prisma Checklist

Search terms 31/3/12

1. HIV

HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR ”sexually transmitted diseases, viral“[MESH:NoExp]

2. Home based

Home-based or home based or homebased OR door to door OR door-to-door OR home care services OR homecare services OR homecare OR home care OR home-care OR home access OR home OR in-home OR domicile

3. Community

Community OR community based OR community-based OR mobile

4. Work place

Work place OR work-place OR workplace OR work OR occupation*

5. VCT

Voluntary Counselling or voluntary Counselling or voluntary Testing or hiv testing or Vct or hbvct or hct

6. Africa

sub-Saharan Africa OR south Africa OR Africa South of the Sahara OR Lesotho OR Swaziland OR Namibia OR Botswana OR Zimbabwe OR Mozambique OR Malawi OR Zambia OR Angola OR Tanzania OR Rwanda OR Burundi OR Democratic republic of Congo OR Republic of Congo OR Uganda OR Kenya OR Ethiopia OR Somalia OR Sudan OR Central African republic OR Cameroon OR Gabon OR Guinea OR Chad OR Nigeria OR Niger OR Togo OR Benin OR Ghana OR Burkina Faso OR Cote d'ivoire OR Ivory coast OR Liberia OR sierra Leone OR Senegal OR Gambia

7. (1 AND 5) AND (2 OR 3 OR 4)
8. (1 AND 5) AND (2 OR 3 OR 4) AND 6
9. Limit 8 to 01/01/2000 to 31/12/2012

PRISMA Checklist

	#	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	M1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	M2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	M3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	M3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	M3-4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	M3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	M3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	M3-4

	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	M3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	M3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	M3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	M3-4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	M3-4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	M3-4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	M3-4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	M4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	M5-7, F1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	M5-7, F6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	M5-7, F8

	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	M5-7, F2-3, F5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	M5-7, F2-3, F5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	M5-7, F8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	M5-7, F4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	M8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	M8-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	M8-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	M10

Chapter 4: Is home-based HIV testing universally acceptable? Findings from a case-control study nested within the HPTN 071 (PopART) trial

Outline of chapter

The first of two case-control studies for this PhD was done to examine the factors associated with the uptake of HB-HTC during the first year of PopART. Presented below is the manuscript for this study which is currently under review with the Journal of Acquired Immune Deficiency Syndrome.

4.1 Abstract

Introduction

The HPTN 071 (PopART) trial is examining the impact of a package including universal testing and treatment on community-level HIV-incidence in Zambia and South Africa. We conducted a nested case-control study to examine factors associated with acceptance of home-based HIV testing and counselling (HB-HTC) delivered by Community HIV-care Providers (CHiPs) in PopART intervention communities.

Methods

Of 295,447 individuals who were offered testing, random samples of individuals who declined HB-HTC (cases) and accepted HB-HTC (controls), stratified by gender and community, were selected. Odds ratios comparing cases and controls were estimated using multi-variable logistic regression.

Results

Data from 642 participants (313 cases, 329 controls) were analysed. There were no differences between cases and controls by demographic or behavioural characteristics including age, marital or socio-economic position. Participants who felt they could be open with CHiPs (AOR:0.46, 95%CI:0.30-0.71, p<0.001); self-reported as not previously tested (AOR:0.64; 95%CI:0.43-0.95, p=0.03); considered HTC at home to be convenient (AOR:0.38, 95%CI:0.27-0.54, p=0.001); knowing others who had accepted HB-HTC from the CHiPs (AOR:0.49, 95%CI:0.31-0.77, p=0.002); or were motivated to get treatment without delay (AOR:0.60, 95%CI:0.43-0.85, p=0.004), were less likely to decline the offer of HB-HCT. Those who self-reported high-risk sexual behaviour were also less likely to decline HB-HCT (AOR: 0.61, 95% CI: 0.39-0.93, p=0.02). Having stigmatising attitudes about HB-HTC was not an important barrier to HB-HCT uptake. Among men, those who reported fear of HIV were more likely to decline HB-HCT (AOR: 2.68, 95%CI: 1.33-5.38, p=0.005).

Discussion and Conclusion

This study, nested within the largest HIV prevention trial to date, provides valuable insights into the acceptability of HB-HTC. Acceptance was associated with lack of previous HIV-testing, positive attitudes about HIV-services/treatment and high sexual-risk perception. Among those contacted, HB-HCT was acceptable across a range of demographic and behavioural characteristics suggesting HB-HCT was “universally” acceptable.

4.2 Introduction

Great advances have been made in controlling the HIV epidemic over time and especially so in the last decade. HIV-incidence worldwide has declined as have HIV related deaths.(1) The number of people receiving anti-retroviral treatment (ART) has increased to 17 million and coverage has reached unprecedented levels even in high-prevalence countries.(2) To gain further ground, a fast-track strategy is called for to achieve UNAIDS' 90-90-90 targets - with benefits for individual health and prevention of transmission.(3-7) The feasibility of treatment as prevention for public health benefit, whereby a sufficiently high proportion of those infected with HIV know their status, start ART and become virally suppressed so that transmission and HIV-incidence may be reduced to a very low level is currently being tested by a number of studies.(8-12) The HPTN 071/ Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) trial is being conducted in 21 communities in Zambia and South Africa (with an average population of >50,000 individuals/community) to examine the impact of Universal Testing and Treatment (UTT) on community-level HIV-incidence.(10, 13)

Despite the progress so far, unless uptake of testing is extensive and inclusive in terms of acceptability to all subsets of the population, the full potential of UTT will not be realised. Home-based HIV-testing and counselling (HB-HTC) has the potential to increase awareness of HIV status in previously undiagnosed individuals in sub-Saharan Africa.(14-17) In theory, offering free HIV-testing services to individuals in their homes provides an opportunity to test with minimal cost (time, effort or financial) to the individual, thereby reducing a number of barriers associated with facility-based HIV-testing. On the other hand, concerns around testing in the household setting and about the value of offering it when individuals feel healthy, may be deterrents to uptake and inhibit universal acceptability.

The PopART intervention includes door-to-door HB-HTC with the aim of achieving universal testing. A case-control (CC) study on a randomly selected subset of those who had accepted (controls) and those who had declined HB-HTC (cases) when offered by Community HIV-care Providers (CHiPs) was carried out, to examine the acceptability of the PopART HB-HTC intervention during the first year of delivery. In addition to exploring demographic, lifestyle, health and behavioural characteristics, we explored differences in perceptions between cases and controls about factors that may affect uptake of HB-HTC. We examined participants' perceptions of HIV services; advantages and disadvantages of accepting HB-HTC for them as individuals and enquired about stigmatising attitudes which may affect uptake. By comparing non-acceptors (cases) and acceptors (controls) of HB-HTC, we hoped to identify any differences and any excluded subsets of the population so that

recommendations could be made to help enable universal knowledge of HIV status be achieved through HB-HTC.

4.3 Methods

The design of the HPTN 071 (PopART) trial has been described previously.(10) Key elements of the trial are shown in Figure 4.1. Working in pairs, the CHiPs (who were community-members employed to work in their communities) were assigned to zones with approximately 500 households to which they delivered the intervention, including HB-HCT. During the first year of the PopART intervention 194,795 individuals in Zambia (88,860 men/105,935 women) and 100,652 in South Africa (44,172 men/56,480 women) were offered HB-HTC by CHiPs in the 14 intervention communities. Of them, 126,208 individuals in Zambia (55,568 men/70,640 women) and 92,375 (40,519 men/51,856 women) in South Africa, accepted testing. Individuals who self-reported HIV-positive status were not routinely offered testing (and are not included in the above figures).

The nested case-control study was done in all the intervention (Arms A and B) communities - 8 in Zambia and 6 in South Africa. The study objectives were to identify differences between non-acceptors (cases) and acceptors (controls) of HB-HTC in the first annual round of HB-HTC in PopART; and to identify reasons for non-acceptance of HB-HTC.

While delivering the PopART intervention, CHiPs captured the details of all individuals who consented to the intervention offered by CHiPs, irrespective of whether or not they accepted HB-HTC, on an electronic register.(10) From the electronic register random samples of non-acceptors (cases) and acceptors (controls) of HB-HTC were selected, with a ratio of 1 case:1 control, an equal number of men and women, and an equal number from each community, to have adequate representation of individuals from all the PopART intervention communities and from both genders. An initial random sample in excess of the number needed to be recruited was selected, in anticipation of difficulties in finding participants – due to mobility of community members with frequent change of address.

To be eligible for the case-control study, participants had to be ≥18 years old, able and willing to provide informed consent and have participated in the first year of the PopART intervention. Belonging to the Population Cohort of the PopART trial (see Figure 4.1) or another PopART case-control study, and already being known to be HIV-infected at the time of the initial CHiP visit were exclusion criteria. HB-HTC acceptance/non-acceptance was defined based on whether a community member had accepted/not-accepted HB-HTC offered by CHiPs at the time of random selection in January (Zambia) and March (South Africa) 2015 – representing one year since the start of the intervention in each country, respectively.

Verbal permission to allow research staff to approach participants was obtained by the CHiP staff who had provided the intervention to individual community members. Written informed consent for study participation was then obtained by study research assistants (RAs). RAs conducted surveys using standardised questionnaires administered electronically. Questionnaire themes were informed by current evidence in the literature or anecdotal local information on factors that may influence uptake of HIV-testing. RAs were kept unaware of participants' case or control status. In the questionnaire, the question about whether the individual had accepted or declined HB-HTC was asked at the end of the interview to minimise interviewer bias.

While monitoring data as part of routine quality assurance, the study team uncovered some irregularities in data collection in South Africa. In-depth internal and independent investigations followed, with oversight from the relevant ethical and regulatory bodies responsible for the study. Consequently, data from one community were not used due to concerns about substantive data irregularities, while in the remaining 5 communities in South Africa a rigorous data-verification process was undertaken to ensure data integrity. Only participants who could be re-contacted and whose data were verified as genuine were retained. The verification process involved confirming the identity of the participant and checking that responses to selected key questions matched responses given during the initial CC visit. No irregularities related to this study were identified in Zambia at any stage.

The final sample size of ~650 participants (1:1 case: control ratio) provides ~80% study power to detect associations with odds ratios of ~1.75 or higher (or ~0.5 or lower), for explanatory variables with 15% prevalence among controls ($\alpha = 0.05$).

Multivariable logistic regression was used to estimate odds ratios, including community and gender in all models to account for the frequency-matched sampling strategy. Age category was also included as an a-priori potential confounding factor. Additional variables (related to demographic or behavioural characteristics but not opinions or perceptions) for which there was at least weak statistical evidence of association with HB-HTC acceptance were included potential confounding variables. Likelihood ratio tests (LRT) were performed to assess the statistical evidence for associations. Evidence of effect modification by gender and country was explored. For variables with 3 or more response categories and potential for a dose-response relationship, test for trends were performed.

The study was approved by the relevant in-country and international ethical review boards (Ethics committees of the University of Zambia, Stellenbosch University and London School of Hygiene and Tropical Medicine).

4.4 Results

As shown in Figure 4.2a, of 910 non-acceptors of HB-HCT (cases) randomly selected to be contacted by CHiPs, 440 (48%) were found and agreed for their contact information to be passed on to the case-control field research assistants (RAs). Of them, 380 (86%) were consented into the study (Figure 4.2a) In South Africa, data were verifiable in 73 of the 140 (52%) cases initially recruited there. There were 313 cases in the final study sample. The proportions recruited among potential controls were similar as shown in Figure 4.2b with 329 controls in the final sample. Data from 642 participants were included in the final analysis – 77% (495) from 8 communities in Zambia and 23% (147) from 5 communities in South Africa (Table-1).

Demographic and household conditions and lifestyle, behavioural and health characteristics

Cases and controls were well balanced by trial arm, community and gender, reflecting the sampling strategy of the study. Participants were distributed fairly evenly across age categories with slightly higher proportions in younger age groups (Table-1). The median age among cases was 32y (IQR: 23-43) and 30y (IQR: 22-40) among controls. The majority of cases and controls were married. While the proportion of participants with higher education was relatively low (12-13%) most had had secondary school education. Most participants were unemployed.

Cases and controls were similarly distributed across almost all the characteristics examined. There were no differences by ethnicity or religion, nor in household conditions, sexual behaviour or health status (including mental health measured by WHO validated Self-Reported Questionnaire (10), circumcision status and history of pregnancies) (Table-1 and from data not shown).

However, participants who had lived in the community for more than 3 years had twice the odds of declining HB-HCT than those who had been resident for less than 3 years (adjusted odds ratio (AOR):2.01,95% confidence interval(95%CI):1.25-3.22,p=0.003).

Neither the number of other household members who were present when HB-HTC was offered to the household, nor the presence of the participant's partner, were associated with acceptance of HB-HCT (Table-1).

Perceptions of HIV-services affecting uptake of HB-HTC

As shown in Table-2 most participants did not know the CHiP prior to the PopART home visit, and there was no association with uptake of HB-HTC. The majority had faith in the confidentiality of services provided by CHiPs, and there was no difference between cases and controls. However, when asked about whether they could talk openly to the CHiPs, participants who "strongly agreed" that they were comfortable talking openly to CHiPs (who provided HB-HTC) were less likely to have declined HB-HTC compared to those who "strongly disagreed/disagreed" (AOR: 0.34, 95%CI: 0.12-

0.91, p=0.03). There is evidence of a trend suggesting that the more strongly a participant agreed that they could talk to the CHiP openly, the less likely they were to have declined HB-HCT (test-for-trend p=0.003). Also, the more strongly participants agreed that providing treatment widely could reduce incidence of new infections, the less likely they were to have declined HB-HCT (test-for-trend p=0.03).

Perceived advantages, disadvantages of HB-HTC (including stigmatizing attitudes which may affect uptake)

When non-acceptors and acceptors were asked (identical) standardized questions about factors that encourage HIV-testing (regardless of whether they actually did), further associations emerged. Individuals who reported never previously testing for HIV, were less likely to have declined HB-HTC (AOR: 0.64, 95%CI: 0.43-0.95, p=0.03). Similarly, those who knew someone who had had an HIV test with the CHiPs (AOR:0.49,95%CI:0.31-0.77, p=0.002); thought they could get treatment without delay if HIV-positive (AOR:0.60,95%CI:0.43-0.85, p=0.004); accepted the CHiP's advice that it was good to have an HIV test (AOR:0.33,95%CI:0.23-0.48, p<0.001); and considered testing at home as convenient (AOR:0.38,95%CI:0.27-0.54, p<0.001) – were less likely to have declined HB-HTC. Participants who indicated that their sexual behaviour put them at risk of HIV (as a reason to test) were also less likely to have declined HB-HTC (AOR: 0.61, 95%CI: 0.39-0.93, p=0.02).

When exploring reasons against accepting HB-HTC, those who reported confidence in being HIV-negative (so there was no need to test) (AOR: 1.61, 95%CI: 1.04-2.51, p=0.03) and reluctance to test again after recent testing (the definition of recency was not specified and left to the interpretation of the participant) (AOR: 1.69, 95%CI: 1.08-2.67, p=0.02), were more likely to decline HB-HCT.

In contrast, other factors such as thinking that HIV is common or concerns about confidentiality of HIV-testing in the household, that might have influenced uptake of testing, were not found to be associated with acceptance (Table-3). There were no important differences between cases and controls in stigmatising attitudes that may affect uptake of HB-HTC (Table-3).

Differences in association by gender and country

There were few differences observed when stratifying associations by gender and country (Supplementary Table 1a and 1b). Men who stated that they feared an HIV-positive test result were more likely to have declined HB-HTC (AOR: 2.68, 95%CI: 1.33-5.38, p=0.005), whereas no such association was noted among women (AOR: 0.84, 95%CI: 0.39-1.80, p=0.65) (LRT for interaction with gender p-value=0.005). In Zambia, participants who had spent one or more nights away from the community in the last 3 months were less likely to have declined HB-HTC (AOR:0.63,95%CI:0.41-0.96,p=0.03) while no evidence of difference was found in South Africa (AOR:1.33,95%CI:0.59-

2.97,p=0.49) (LRT for interaction with country p-value=0.05). There were also country differences in response to a question about whether lack of time due to work commitments was a reason to decline HB-HTC (LRT for interaction with country p-value=0.03). In South Africa, those who declined HB-HCT were much more likely to state this as a reason not to test than those who accepted, although the 95% CI was wide for the estimated adjusted odds ratio (AOR:4.73, 95%CI:1.02-21.98, p=0.03). There was no such association in Zambia (AOR: 0.95, 95%CI: 0.61-1.47, p=0.83), (LRT for interaction with country p-value=0.03)

4.5 Discussion

Our study provides evidence from large urban communities that were targeted to receive universal testing (and in Arm A communities, universal treatment as well) (Figure 4.1). UTT has the potential to influence acceptability and uptake of HIV-testing and only one other quantitative study to our knowledge has reported findings from a setting providing UTT. This study was on data from a much smaller trial than PopART, set in rural South Africa with 10 clusters and an average population size of approximately 1000 individuals/cluster), and only a few potential factors associated with the uptake of HB-HTC were described.(18) While there are descriptive studies of acceptors of testing and HB-HTC, relatively few studies have directly compared acceptors with non-acceptors of HB-HTC, and in-depth quantitative data on reasons to decline are limited. (18-21) HB-HTC acceptance has been shown to be associated with age (greater than 25y) and female gender in Kenya,(19) and low socio-economic position in a the setting of a small island in Lake Malawi.(20) Other data have shown no association between HB-HCT uptake and demographic or socio-economic position.(18) Prior knowledge of HIV status (known HIV-infected or believing one-self to be uninfected based on a previous HIV-negative test result), and not being ready to find out, have been found as reasons to decline HB-HTC in rural South Africa.(21) Others have reported little that is significantly different between those who accepted and those who did not accept HB-HTC.(18)

In our study in 13 large urban communities in Zambia and South Africa, we found that among those who were encountered and offered HB-HTC, there were no fundamental differences based on demographic, lifestyle, behavioural or health characteristics, between those who accepted (controls) and those who declined HB-HCT (cases). Our data indicate that there were no specific subsets of the population who were systematically less likely to accept testing, once contacted, suggesting that HB-HTC has the potential to be universally acceptable to those offered it. To achieve universal coverage, innovative means must be explored to ensure everyone in the community (or as high a proportion as possible) is contacted so that they can be offered HB-HTC.(22)

In contrast, cases and controls did seem to differ in perceptions held about issues related to HIV and HIV-services. Most participants gave favourable responses regarding HIV services, and those who held positive views about the CHiPs were less likely to have declined HB-HTC. There were several factors that encouraged testing at the individual level. Participants who had not tested for HIV previously were more likely to accept HB-HTC in contrast to those who had previously tested HIV-negative or had tested recently and felt that repeat testing was not warranted.

Participants who declined HB-HCT were less positive about treatment for HIV than those who accepted. Further, those who declined were more likely to hold the view that they were not at risk of HIV and it was therefore not a reason for them to test. Low-risk perception as a reason not to test was also observed by Naik et al.(23) Yet when we explored self-reported sexual behaviour of participants there is no evidence that those who declined HB-HCT were at lower risk based on the number of partners in the last 12 months (Table-1), number of lifetime partners or age at sexual debut (data not shown).

Other views that might have been assumed to encourage or discourage testing had no association with observed acceptance of HB-HTC. For example, concerns about confidentiality with testing in the home, or the presence of other household members during delivery of HB-HTC (including partner), were not associated with acceptance and so these factors did not appear to inhibit testing. Contrary to other studies (23), “not feeling ready to find out” his/her HIV status was not found to be associated with acceptance in our study. Having stigmatising attitudes about HB-HTC was also not seen to be an important barrier to uptake in our setting.

We found surprisingly few differences between responses given by men and women. However, the data do suggest that among men, fear of an HIV-positive result was associated with HB-HTC non-acceptance.

Further research is needed to explain some study findings, including the association of longer duration lived in the community with non-acceptance, or the finding that greater mobility is associated with increased likelihood of acceptance in Zambia. Several of the communities studied have been exposed to HTC campaigns in the past. Individuals who have been resident for longer periods may have been tested before and therefore declined HB-HTC when offered by PopART CHiPs. In contrast, mobility is associated with higher sexual risk (24) and individuals who are mobile may be more inclined to accept HB-HTC if they feel at risk of HIV. Social science research is being conducted on a subset of the participants from this case-control study and in-depth interviews may provide more nuanced explanations.

Our study had some limitations to consider. To comply with ethical principles and good research practice, only individuals who were encountered and agreed to participate in the PopART intervention, and who were re-contacted and provided informed consent for the CC study, could be recruited as participants. Due to high mobility in the study communities, randomly selected individuals from the CHiP data-base were often difficult to trace, to ask permission for contact by the research team. As such, it may be that the study population is not representative of all community members and our results (like much of the published data from similar study settings) must be interpreted in the light of this limitation.

Finally, in common with most research using self-reported data, reporting bias is possible. Social desirability may have played a part in the responses given, although we would not expect this to be differential based on whether an individual had accepted HB-HTC for most themes studied. We also minimised observer bias by keepings research assistants unaware of case/control status of participants until the end of the questionnaire.

However, our study also had several strengths. There was no single or obvious hypothesis being tested, so respondents were unlikely to give responses in order to conform to (or contradict) such a hypothesis. In contrast to much of the existing literature on acceptability of HIV-testing, our study is specific to the context of attempting to provide universal testing and at large scale. Further, we directly compared those who accepted HB-HTC with those who did not to provide evidence of differences rather than simply describing individuals without comparators. Also, by frequency matching our study sample by gender we ensured an adequate sample of men who are often under-represented in studies of HIV test uptake despite (or because of) the fact that they are more frequently non-engagers with HIV services. The response rates between cases and controls were similar indicating that there was no evidence of differential selection of potential participants by case/control status. Finally, the study covered an extensive range of themes. The null findings make an important contribution to identifying which areas may be less important when designing public health information to encourage HB-HCT.

While firm evidence of causality cannot be inferred from this observational study, our study findings provide opportunities for tailoring services and public-health messaging to extend the reach of HB-HTC, to those who may currently be avoiding it. Our first key recommendation in this light is to re-inforce the importance of testing irrespective of self-held perceptions of risk of HIV, especially where universal knowledge of HIV status is sought. WHO guidelines do not recommend re-testing to cover a “window-period” (25) and it is reasonable not to re-test following a test in the last 3 months. However, if there is any potential for on-going exposure repeat and on-going testing (e.g., annually)

should be encouraged from a public-health point of view. The failure to re-test because of a past HIV-negative result may be complacent, especially in high prevalence settings. Data from PopART intervention delivery indicate high acceptability of HB-HTC provided by CHiPs.(26) Data from this study, highlight the benefits to be gained by maximising the acceptability of the cadre of staff delivering HB-HTC, and which may help us reach universality. Similarly, promoting the benefits of treatment may have benefits for uptake of testing. Among men, fear of HIV seems to influence test uptake and efforts must be made to understand and mitigate it. We recommend that there should be investment in health promotion which de-mystifies HIV – through expansion of channels to target men (health promotion aligned with sporting events and activities, or tailored male-friendly services, for instance).

Conclusion:

This case-control study, which is nested within the largest HIV prevention trial to date, provides valuable insights into the acceptability of HB-HTC. HB-HTC has the potential to be universally acceptable to those who can be contacted and offered it. We have identified perceptions and opinions held by community members that could help tailor public health messaging with a view to achieving universal knowledge of HIV status in high prevalence settings.

Conflicts of interests:

We declare that we have no conflicts of interests.

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Authors' contributions:

KS designed the study, led on writing and revising the paper and led on the statistical analysis of the data, with oversight from RH. CM, CMM, HM and GH were involved with leading field data collection and ensuring the quality of data. AS led on programming of study tools and had over-sight of the random selection of participants and data management. JH provided expert advice to the stigma related content of the study. SF and HA provided specific advice on statistical methods and study design/conduct, respectively. All authors contributed to the writing of the paper and have read and approved the final manuscript.

4.6 References

1. UNAIDS. Fast-track: Ending the AIDS Epidemic by 2030. http://wwwunaidsorg/sites/default/files/media_asset/JC2686_WAD2014report_enpdf. 2015;Accessed on 28th May 2015.
2. UNAIDS. 90-90-90 On the right track towards the global target. http://wwwcfenetubcca/sites/default/files/uploads/IAS2016/90_90_90_Progress_ReportFINALpdf. 2016;Accessed on 27th July 2016.
3. UNAIDS. Fast-track: Ending the AIDS Epidemic by 2030. http://wwwunaidsorg/sites/default/files/media_asset/JC2686_WAD2014report_enpdf. 2015;Accessed on 11th January 2016.
4. Cohen M, Chen Y, M. M. Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Vancouver. 2015;Oral Presentation(Abstract MOAC0101LB).
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England journal of medicine. 2011;365(6):493-505.
6. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The New England journal of medicine. 2015;373(9):795-807.
7. TEMPRANO ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.
8. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657):48-57.
9. BCPP Study Group. Botswana Combination Prevention Project (BCPP). https://clinicaltrialsgov/ct2/show/NCT01965470. 2013; Accessed on 26th November 2015.
10. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.
11. SEARCH Study Team. Sustainable East Africa Research in Community Health (SEARCH). https://clinicaltrialsgov/ct2/show/NCT01864603?term=NCT01864603&rank=1. 2013;Accessed on 26th November 2015.
12. The MaxART Programme. http://stopaidsnoworg/treatment-prevention. 2011;Accessed on 20th July 2016.
13. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. PloS one. 2014;9(1):e84511.
14. Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N. Uptake of Home-Based Voluntary HIV Testing in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. PLoS Med. 2012;9(12):e1001351.
15. Sharma M, Ying R, Tarr G, Barnabas R. Systematic review and meta-analysis of community and facility-based HIV testing to address linkage to care gaps in sub-Saharan Africa. Nature. 2015;528(7580):S77-85.
16. Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med. 2013;10(8):e1001496.
17. Iwuji C, Orne-Gliemann J, Balestre E, Larmarange J, Thiebaut R, Tanser F, et al. The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. 21st International AIDS Conference, Durban. 2016;abstract FRAC0105LB.

18. Iwuji CC, Orne-Gliemann J, Larmarange J, Okesola N, Tanser F, Thiebaut R, et al. Uptake of Home-Based HIV Testing, Linkage to Care, and Community Attitudes about ART in Rural KwaZulu-Natal, South Africa: Descriptive Results from the First Phase of the ANRS 12249 TasP Cluster-Randomised Trial. PLoS Med. 2016;13(8):e1002107.
19. Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, et al. Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial. J Acquir Immune Defic Syndr. 2010;55(2):245-52. doi: 10.1097/QAI.0b013e3181e9e069.
20. Helleringer S, Kohler HP, Frimpong JA, Mkandawire J. Increasing uptake of HIV testing and counseling among the poorest in sub-Saharan countries through home-based service provision. J Acquir Immune Defic Syndr. 2009;51(2):185-93. doi: 10.1097/QAI.0b013e31819c1726.
21. Naik R, Tabana H, Doherty T, Zembe W, Jackson D. Client characteristics and acceptability of a home-based HIV counselling and testing intervention in rural South Africa. BMC Public Health. 2012;12:824.(doi):10.1186/471-2458-12-824.
22. Yang B, van Deventer D, Dunbar R, Bock P, Griffith S, Ayles H, et al. Working evening and weekend schedules is effective in reaching more men for home-based HIV testing: findings from HPTN 071 (PopART) in South Africa. 21st International AIDS Conference, Durban. 2016.
23. Naik R, Tabana H, Doherty T, Zembe W, Jackson D. Client characteristics and acceptability of a home-based HIV counselling and testing intervention in rural South Africa. BMC Public Health. 2012;12:824.
24. Weine SM, Kashuba AB. Labor migration and HIV risk: a systematic review of the literature. AIDS and behavior. 2012;16(6):1605-21.
25. World Health Organization. Consolidated guidelines on HIV testing services. http://appswhoint/iris/bitstream/10665/179870/1/9789241508926_engpdf?ua=1&ua=1. 2015;Accessed on 26th July 2016.
26. Hayes R, HPTN 071 (PopART) Study Team. Reaching the 90-90-90 target: Lessons from HPTN 071 (PopART). http://wwwtreatmentaspreventionworkshoporg/un-90-90-90-target-workshop-videos. International Treatment as Prevention Workshop, 2015;Accessed on 4th November 2016.

Figure 4.1: PopART Trial Schema

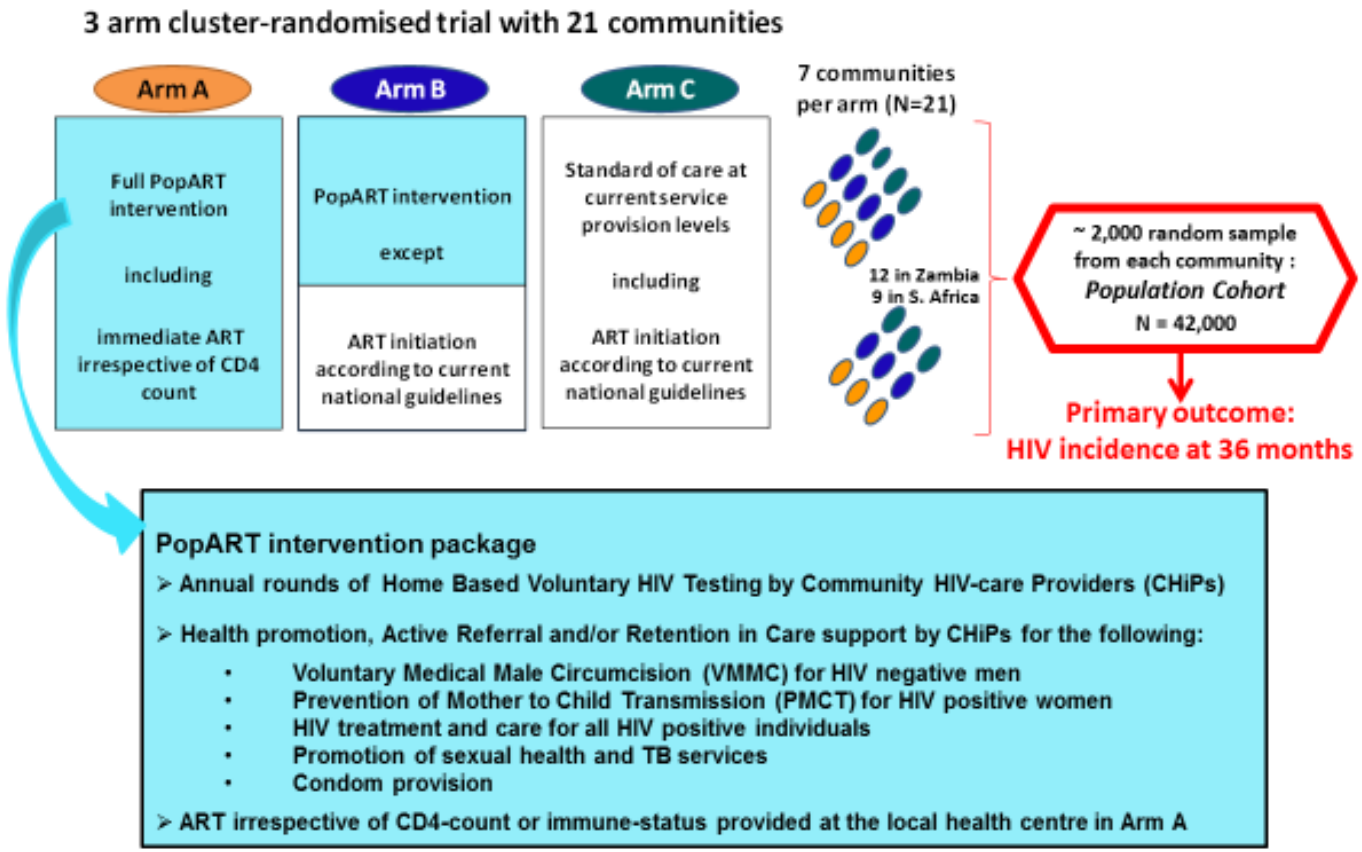

Figure 4.2a: Case (non-acceptor) selection process and sampling fraction

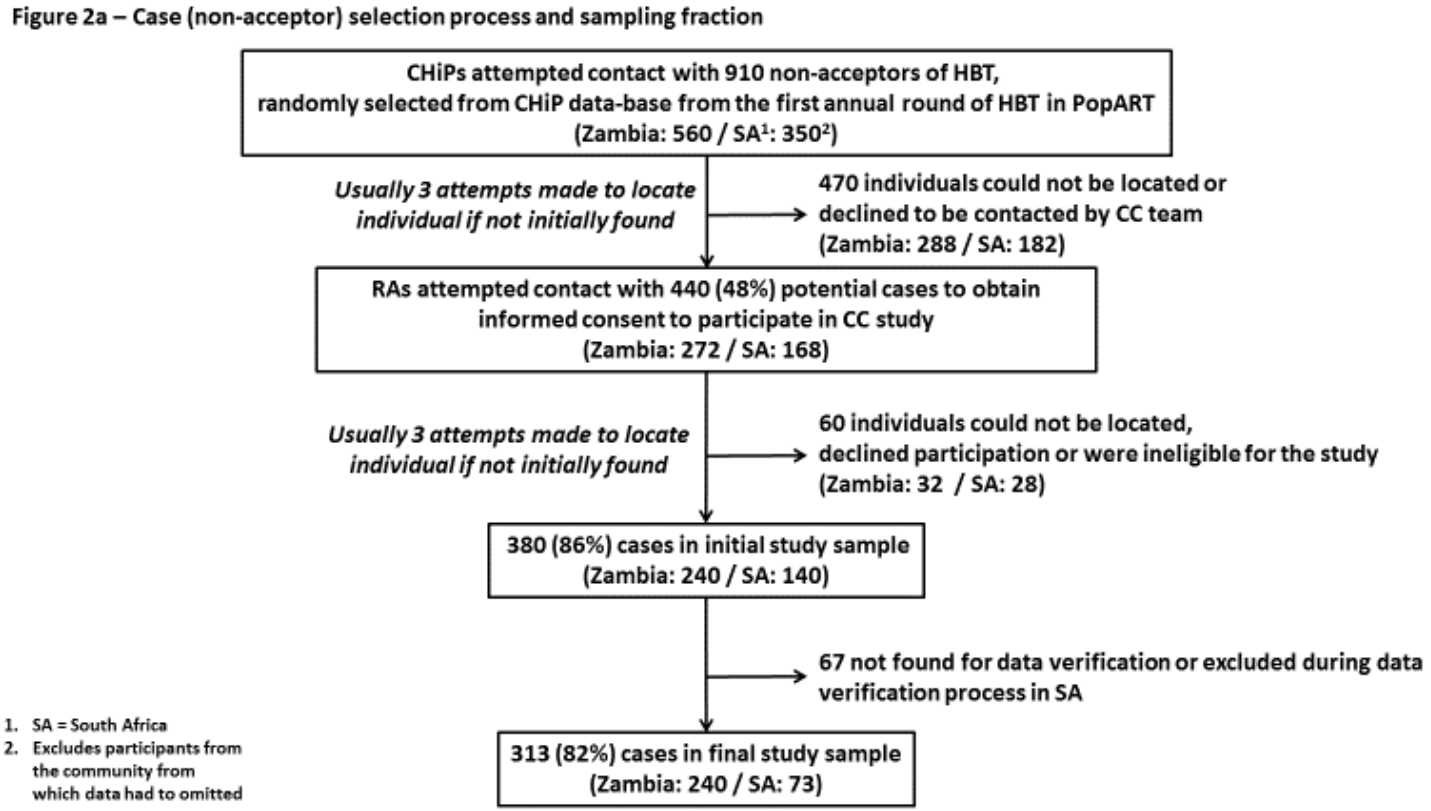

Figure 4.2b: Control (acceptor) selection process and sampling fraction

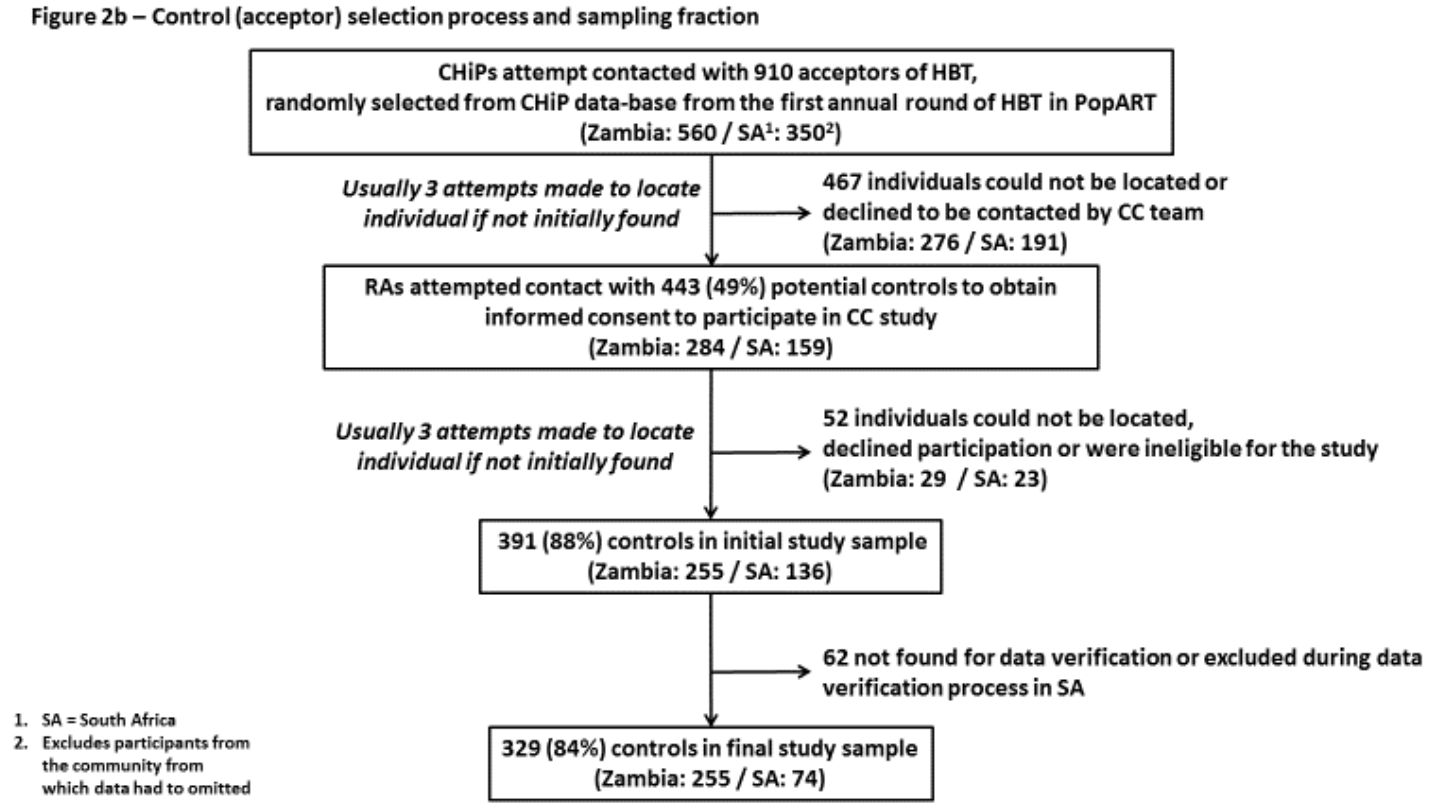

Table 4.1: Demographic and household conditions, and lifestyle, behavioural and health characteristics of cases and controls

	Cases (Non-acceptors) N (%)	Controls (Acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio [3]	*LRT [2] p-value*, 95 % Confidence Interval
Total	313	329				
Gender						
Male	153 (49)	150 (46)				
Female	160 (51)	179 (54)				
Demographic characteristics						
Age category						P_{trend} [4] *0.57*
18 – 24 years	95 (30)	110 (33)	1	*0.16*	1	*0.34*
25 – 34 years	79 (25)	98 (30)	0.93	0.62-1.14	0.87	0.57-1.32
35 – 44 years	73 (23)	54 (16)	1.55	0.98-2.45	1.35	0.84-2.15
≥ 45 years	66 (21)	67 (20)	1.17	0.74-1.83	1.00	0.63-1.59
Marital status						
Never married	104 (33)	106 (32)	1	*0.63*	1	*0.56*
Currently married	162 (52)	178 (54)	0.89	0.62-1.27	0.78	0.50-1.23
Previously married [5]	47 (15)	45 (14)	1.08	0.65-1.81	0.85	0.46-1.58
Educational attainment						P_{trend} [4] *0.21*
Primary (Grade 0-7)	86 (27)	94 (29)	1	*0.81*	1	*0.62*
Junior secondary (Grade 8-9)	72 (23)	81 (25)	0.99	0.64-1.55	1.13	0.71-1.80
Senior secondary (Grade 10-12)	115 (37)	114 (35)	1.12	0.74-1.71	1.32	0.83-2.10
Higher education	40 (13)	40 (12)	1.28	0.72-2.29	1.38	0.75-2.51
Employment						
None	165 (53)	186 (57)	1	*0.36*	1	*0.52*
Casual/seasonal/occasional	43 (14)	44 (13)	1. 00	0.61-1.66	0.97	0.57-1.64
Self employed	49 (16)	37 (11)	1.56	0.93-2.61	1.46	0.85-2.49
Formal wage	56 (18)	62 (19)	0.97	0.63-1.51	1.00	0.63-1.60
Household conditions						
SES (PCA[6] of HH factors & assets[7])						
Lower	152 (49)	170 (52)	1	*0.10*	1	*0.15*
Higher	161 (51)	159 (48)	1.36	0.94-1.96	1.31	0.90-1.89
Number of other HH members present when CHiP offered HBT						P_{trend} [4] *0.47*
0	113 (37)	122 (38)	1	*0.90*	1	*0.73*
1	83 (27)	87 (27)	0.93	0.62-1.42	0.98	0.64-1.49
≥ 2	107(35)	112 (35)	0.91	0.60-1.37	0.85	0.56-1.30
Was partner present when participant offered CHiP HBT?						
N	237 (78)	249 (78)	1	*0.53*	1	*0.47*
Y	66 (22)	72 (22)	0.87	0.56-1.34	0.84	0.52-1.35
Lifestyle, behavioural and health factors						
Years lived in the community						
≤ 3	33 (11)	63 (19)	**1**	***0.002***	**1**	***0.003***
≥ 4	278 (89)	261 (81)	**2.09**	**1.31-3.32**	**2.01**	**1.25-3.22**
Any nights spent away from home in last 3m						
N	159 (58)	155 (52)	1	*0.19*	1	*0.17*
Y	117 (42)	144 (48)	0.79	0.55-1.13	0.77	0.54-1.19
Number of partners in last 12m						
0	64 (23)	70 (23)	1	*0.87*	1	*0.79*
1	185 (65)	204 (67)	0.92	0.61-1.38	0.94	0.62-1.43
≥ 2	35 (12)	31 (10)	1.09	0.59-2.01	1.15	0.61-1.43
Audit Score						
Audit Score ≤ 7	242 (77)	260 (79)	1	*0.74*	1	*0.56*

Audit Score ≥ 8	71 (23)	69 (21)	1.07	0.71-1.61	1.13	0.75-1.72
Unwell in last 12m						
N	208 (67)	224 (68)	1	*0.74*	1	*0.59*
Y	104 (33)	105 (32)	1.06	0.75-1.50	1. 10	0.77-1.58
Any form of violence (verbal/physical/sexual) from any partner in last 12m (among women)						
No	119 (74)	130 (73)	1	*0.82*	1	*0.90*
At least once	41 (26)	49 (27)	0.94	0.56-1.57	0.98	0.57-1.67

1. *A priori* adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. P value for test for trend
5. Previously married = separated/divorced/widowed
6. Principal components analysis
7. HH factors detailed house structure, water, sanitation, electricity and cooking fuel used; assets listed were: working cell-phone, bicycle, motorcycle or scooter, car/bakkie, electricity to house, television set, fridge/freezer, radio, computer/laptop, CD or MP3 player, stereo/cassette/other music player, “none of the above”

Table 4.2: Participants' perceptions of HIV service factors affecting uptake of testing

	Cases (Non-acceptors) N (%)	Controls (Acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio [3]	*LRT [2] p-value*, 95 % Confidence Interval
HIV service factors affecting uptake of testing						
Was the CHiP known to the participant prior to offer of HBT?						
N	265 (85)	272 (83)	1	*0.61*	1	*0.49*
Y	48 (15)	57 (17)	0.88	0.56-1.40	0.85	0.54-1.35
Do you think confidentiality will be maintained by the CHiP? [4]						p_{trend} [5] *0.16*
Strongly disagree/disagree	15 (5)	18 (5)	1	*0.10*	1	*0.16*
Agree	98 (31)	82 (25)	1.49	0.69-3.22	1.42	0.65-3.10
Strongly agree	200 (64)	229 (70)	0.95	0.46-2.00	0.91	0.43-1.94
Was the CHiP someone you could talk to openly? [4]						p_{trend} [5] *0.003*
Strongly disagree/disagree	12 (4)	7 (2)	1	*0.002*	1	*0.001*
Agree	92 (29)	70 (21)	0.81	0.29-2.24	0.70	0.25-1.94
Strongly agree	209 (67)	252 (77)	0.40	0.15-1.07	**0.34**	**0.12-0.91**
Providing treatment for as many HIV infected people as possible can help reduce new HIV infections happening in your community [4]						p_{trend} [5] *0.03*
Strongly disagree	19 (6)	21 (6)	1	*0.09*	1	*0.04*
Disagree	46 (15)	31 (9)	1.54	0.70-3.38	1.63	0.73-3.65
Agree	91 (29)	89 (27)	1.14	0.55-2.35	1.11	0.54-2.31
Strongly agree	156 (50)	188 (57)	0.82	0.42-1.61	0.78	0.39-1.52
Group counselling for HH members (including offer of HIV test) in the home is acceptable [4]						p_{trend} [5] *0.93*
Strongly disagree	41 (13)	43 (13)	1	*0.80*	1	*0.80*
Disagree	31 (10)	34 (10)	1.02	0.53-1.98	0.97	0.50-1.93
Agree	86 (28)	83 (25)	1.20	0.68-2.13	1.21	0.68-2.16
Strongly agree	154 (49)	169 (51)	0.97	0.58-1.61	0.98	0.58-1.63

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. There were very few responses in the "strongly disagree" and "disagree" categories for these questions, responses are therefore grouped as shown to be more meaningful/increase power
5. p-value for test for trend

Table 4.3: Participants' perceptions of advantages and disadvantages of accepting of HB-HTC

	Cases (Non-acceptors) N (%)	Controls (Acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio [3]	*LRT [2] p-value*, 95 % Confidence Interval
Individual level factors encouraging testing						
When offered a test by the PopART CHiP, did any of the following encourage you towards having an HIV test?						
I have never had an HIV test and wanted to learn my status						
N	247 (79)	237 (72)	**1**	***0.03***	**1**	***0.03***
Y	65 (21)	92 (28)	**0.65**	**0.44-0.96**	**0.64**	**0.43-0.95**
HIV is common in this community so I thought I should test to check my status						
N	217 (70)	223 (68)	1	*0.46*	1	*0.37*
Y	95 (30)	106 (32)	0.87	0.60-1.27	0.84	0.57-1.23
Convenience of having an HIV test at home encouraged me to test						
N	164 (53)	104 (32)	**1**	***<0.001***	**1**	***0.001***
Y	148 (47)	225 (68)	**0.39**	**0.28-0.55**	**0.38**	**0.27-0.54**
Many people I know had tested with a CHiP so I wanted to as well						
N	263 (84)	246 (75)	**1**	***0.001***	**1**	***0.002***
Y	49 (16)	83 (25)	**0.49**	**0.32-0.77**	**0.49**	**0.31-0.77**
Accepted CHiP advice that it was a good idea to test						
N	154 (49)	89 (27)	**1**	***<0.001***	**1**	***<0.001***
Y	158 (51)	240 (73)	**0.35**	**0.24-0.49**	**0.33**	**0.23-0.48**
Getting treatment without delay if I tested and was HIV-positive (encouraged me to test)						
N	149 (48)	119 (36)	**1**	***0.004***	**1**	***0.004***
Y	163 (52)	210 (64)	**0.61**	**0.44-0.86**	**0.60**	**0.43-0.85**
My sexual behaviour has put me at risk of HIV						
N	263 (84)	257 (78)	**1**	***0.02***	**1**	***0.02***
Y	49 (16)	72 (22)	**0.61**	**0.40-0.94**	**0.61**	**0.39-0.93**
Individual level factors discouraging testing						
When offered a test by the PopART CHiP, did any of the following discourage you from having an HIV test?						
I had difficulty with the time it would take - because of my livelihood/job						
N	226 (72)	247 (75)	1	*0.42*	1	*0.52*
Y	86 (28)	82 (25)	1.18	0.79-1.75	1.14	0.76-1.71
I was worried someone would find out I was having an HIV test						
N	305 (98)	313 (95)	1	*0.08*	1	*0.11*
Y	7 (2)	16 (5)	0.45	0.18-1.12	0.48	0.19-1.22
I did not want to find out my HIV status because I was afraid of a positive test result						
N	263 (84)	288 (88)	1	*0.19*	1	*0.09*
Y	49 (16)	41 (12)	1.38	0.85-2.22	1.53	0.94-2.50
I was confident I was HIV-negative and didn't need to test						
N	242 (78)	274 (83)	**1**	***0.05***	**1**	***0.03***
Y	70 (22)	55 (17)	**1.53**	**1.00-2.34**	**1.61**	**1.04-2.51**
I already had a test recently and did not want to test again						
N	254 (81)	287 (87)	**1**	***0.03***	**1**	***0.02***
Y	58 (19)	42 (13)	**1.63**	**1.05-2.53**	**1.69**	**1.08-2.67**
I am not ready to find out my HIV status						
N	267 (86)	289 (88)	1	*0.15*	1	0.12
Y	45 (14)	40 (12)	1. 50	0.86-2.64	1.57	0.88-2.77
I just did not want to find out my HIV status (no particular reason)						
N	279 (89)	298 (91)	1	*0.40*	1	0.40
Y	33 (11)	31 (9)	1.32	0.70-2.48	1.32	0.69-2.50
Stigmatising attitudes which may affect uptake of testing						
People are hesitant to take an HIV test due to fear of other people's reaction if the test result is positive for HIV						P_{trend} [4] *0.18*
Strongly disagree	69 (22)	72 (22)	1	*0.10*	1	*0.10*
Disagree	54 (17)	49 (15)	1.03	0.57-1.86	0.96	0.52-1.76

Agree	99 (32)	116 (35)	1.28	0.77-2.13	1.20	0.71-2.02
Strongly agree	90 (29)	92 (28)	0.73	0.45-1.18	0.68	0.42-1.12
People sometimes talk badly about people who have had or who are thought to have had an HIV test						*P_{trend} [4] 0.79*
Strongly disagree	69 (22)	72 (22)	1	*0.78*	1	*0.83*
Disagree	54 (17)	49 (15)	1.10	0.64-1.87	0.99	0.58-1.71
Agree	99 (32)	116 (35)	0.86	0.53-1.39	0.83	0.51-1.35
Strongly agree	90 (29)	92 (28)	1.02	0.62-1.67	0.98	0.59-1.62
People may think that I have been immoral/irresponsible as the reason behind having an HIV test						*P_{trend} [4] 0.53*
Strongly disagree	129 (41)	146 (44)	1	*0.60*	1	*0.53*
Disagree	69 (22)	77 (23)	0.96	0.62-1.48	0.90	0.57-1.40
Agree	68 (22)	60 (18)	1.34	0.82-2.21	1.33	0.80-2.20
Strongly agree	46 (15)	46 (14)	1.05	0.62-1.79	1.04	0.60-1.79
People receive verbal abuse or insults because of having an HIV test						*P_{trend} [4] 0.90*
Strongly disagree	43 (14)	44 (13)	1	*0.61*	1	*0.82*
Disagree	73 (23)	84 (26)	1.33	0.85-2.06	1.21	0.77-1.90
Agree	78 (25)	65 (20)	1.03	0.65-1.62	1.02	0.64-1.62
Strongly agree	118 (38)	136 (41)	1.04	0.61-1.77	0.97	0.56-1.69

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. p value for test for trend

Supplementary Table 4.1a: Factors with effect modification by gender, of association with case/control status,

	Controls (Acceptors) N (%)	Cases (Non-acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value*, 95 % Confidence Interval	Controls (Acceptors) N (%)	Cases (Non-acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value*, 95 % Confidence Interval
	Men						**Women**					
Individual level factors affecting testing												
I did not want to find out my HIV status because I was afraid of a positive test result											$p_{effect\ modification}$ [4] *0.02*	
N	132 (88)	119 (78)	**1**	***0.01***	**1**	***0.005***	156 (87)	144 (90)	1	*0.47*	1	*0.65*
Y	18 (12)	33 (22)	**2.27**	**1.16-4.44**	**2.68**	**1.33-5.38**	23 (13)	16 (10)	0.76	0.36-1.60	0.84	0.39-1.80
I just did not want to find out my HIV status (no particular reason)											$p_{effect\ modification}$ [4] *0.05*	
N	131 (86)	138 (92)	**1**	***0.03***	**1**	**0.02**	71 (97)	71 (96)	1	*0.27*	1	*0.20*
Y	21 (14)	12 (8)	**2.58**	**1.09-6.10**	**2.83**	**1.17-6.86**	3 (2)	3 (4)	0.56	0.20-1.59	0.50	0.17-1.47
People sometimes talk badly about people who have had or who are thought to have had an HIV test											$p_{effect\ modification}$ [4] *0.02*	
Strongly disagree	32 (21)	32 (21)	1	*0.39*	1	*0.43*	37 (23)	40 (22)	1	*0.05*	1	***0.04***
Disagree	25 (16)	20 (13)	1.06	0.47-2.37	1.00	0.44-2.26	29 (18)	29 (16)	1.04	0.50-2.16	0.94	0.44-1.98
Agree	58 (38)	48 (32)	1.26	0.63-2.53	1.24	0.61-2.54	41 (26)	68 (38)	0.54	0.27-1.08	0.50	0.25-1.02
Strongly agree	37 (24)	50(33)	0.72	0.34-1.50	0.71	0.34-1.51	53 (33)	42 (23)	1.28	0.65-2.52	1.25	0.62-2.52

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. LRT p-value indicating evidence of effect modification by gender

Supplementary Table 4.1b: Factors with effect modification by country, of association with case/control status

	Controls (Acceptors) N (%)	Cases (Non-acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value*, 95 % Confidence Interval	Controls (Acceptors) N (%)	Cases (Non-acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value*, 95 % Confidence Interval
	Zambia						**South Africa**					
Demographic characteristics												
Any nights spent away from home in last 3m											$p_{effect\ modification}$ [4] *0.05*	
N	110 (54)	100 (44)	**1**	***0.03***	**1**	***0.03***	49 (67)	55 (75)	1	*0.26*	1	*0.49*
Y	93 (46)	126 (56)	**0.64**	**0.43-0.97**	**0.63**	**0.41-0.96**	24 (33)	18 (25)	1.53	0.72-3.29	1.33	0.59-2.97
Individual level factors affecting testing												
I had difficulty with the time it would take - because of my livelihood/job											$p_{effect\ modification}$ [4] *0.03*	
N	176 (69)	162 (68)	**1**	***0.87***	**1**	***0.83***	7 1 (96)	3 (4)	1	*0.08*	1	*0.03*
Y	79 (31)	77 (32	**1.04**	**0.68-1.58**	**0.95**	**0.62-1.47**	64 (88)	9 (12)	3.22	0.79-1.321	4.73	1.02-21.98

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. LRT p-value indicating evidence of effect modification by country

Chapter 5: The cascade-of-care following community-based detection of HIV – a systematic review with 90-90-90 targets in sight

Outline of chapter

This chapter presents a second systematic review which was carried out as part of this PhD to further understand the factors associated with the uptake of UTT. In order to achieve the goal of HIV-incidence reduction through UTT, a high proportion of individuals who are identified as PLWH have to link to care and initiate treatment in a timely fashion. A systematic review which explored the cascade of care following HIV diagnosis was done, and it was focused on the cascade following HTC in the community as home-based and mobile testing are the main interventions used to achieve universal testing.

Presented below is the manuscript which is under consideration by the Journal of the International AIDS Society following re-submission after receiving peer reviewer comments.

5.1 Abstract

Introduction

We aimed to establish how effective community-based HIV testing services (HTS), including home and mobile-based HIV testing services (HB-/M-HTS), are in improving care in sub-Saharan Africa (SSA), with a view to achieving the 90-90-90 targets.

Methods

We conducted a systematic review of published literature from 2006-16 which reported on the proportion of individuals who link-to-care and/or initiate ART after detection with HIV through community-based testing. A meta-analysis was deemed inappropriate due to heterogeneity in reporting.

Results

Twenty-two studies from 6 SSA countries were included in the final review – 12 HB-HTS, 8 M-HTS, 2 combined HB-/M-HTS. Proportions linked-to-care over 1-10 months ranged from 14-96% for HB-HTS and 10-79% for M-HTS, with most studies reporting outcomes over short periods (3 months). There was variability in definitions of outcomes, numerators/denominators and observation periods. Outcomes varied between studies even for similar time-points since HTS. Previously diagnosed individuals appear more likely to link-to-care than those who reported being newly-diagnosed. Point-of-care (POC) CD4-counts at the time of HTS did not achieve higher proportions linking-to-care or initiating ART. Similarly, follow-up visits to HIV-positive individuals did not appear to enhance linkage to care overall.

Fewer studies reported ART-related outcomes following community-based testing especially retention on ART or viral suppression on treatment. Proportions initiating ART ranged from 23-85% (17 studies - 9 of them involving <50 individuals); 6-months after ART initiation, 76% were still on ART (one study); and viral suppression was 77-85% (two studies).

Discussion and Conclusion

This systematic review summarises the available data on linkage to care/ART initiation following community-based detection of HIV, to help researchers and policy makers evaluate findings. We have identified important methodological inconsistencies in the literature quantifying the cascade of care, which hamper comparisons. We recommend that standardised measures of reporting of steps on the cascade of care are needed, to measure progress against targets and compare across settings.

In contrast to the benefits of POC CD4-counts in clinics, use in the community was not a facilitator for linkage to care or ART initiation. It appears that individuals diagnosed in the community need time before they are ready to link-to-care/initiate ART. The available evidence suggests that different approaches to community-based HTS including HB-HTS and M-HTS, are equally effective in achieving linkage to care and ART initiation.

5.2 Introduction

UNAIDS 90-90-90 targets aim to ensure that by 2020, 73% of people living with HIV (PLWH) are virally suppressed.(1) The benefits of early treatment for those who are infected, and for the prevention of onward transmission, are now firmly established.(2-4)

Using out-of-facility, community-based approaches to increase knowledge of HIV status in sub-Saharan Africa (SSA) towards achieving the first-90, now seems ever more attainable.(5-8) These approaches detect infected individuals earlier in the course of infection. The benefits may conversely pose challenges for timely linkage to care. Individuals who feel well may not be ready to access care at health facilities even when provided with a diagnosis. While community-HTS reduces barriers for testing, the challenges associated with health facilities remain and individuals identified by community-HTS may be less likely and/or take longer to link-to-care.

Linkage to care should result ultimately in viral suppression among people living with HIV (PLWH). The 90-90-90 targets provide a standard against which performance can be measured. This systematic review examines published evidence from sub-Saharan Africa on linkage to care, initiation of ART and retention/viral suppression if reported, following out-of-facility community-based detection of HIV, with the 90-90-90 targets in mind - in particular the second- and third-90s.

5.3 Methods

We conducted a systematic review according to the criteria in PRISMA guidelines (Supplementary Material) and devised a pre-defined search protocol. Our primary objective was to determine what proportion of individuals, detected with HIV through community-based testing, link into HIV care and/or start ART. We use the term HIV detection to refer to HIV diagnosis through community-based HIV testing services (HTS) or self-report of known HIV-positive status at the time of HTS.

Search strategy

We summarised studies that described the cascade of care following HIV detection through community-based approaches (namely home-based HTS (HB-HTS) or mobile/outreach HTS (M-HTS) approaches which use mobile units or temporary structures), in SSA. We searched Pubmed, Embase and Global Health electronic databases. We developed a broad compound search strategy that combined terms for "home based", "mobile", "community", "work-place", "school-based", "self-testing" "HIV" and "voluntary counselling and testing" (Supplementary Material). We also manually searched the bibliographies of relevant articles. We screened studies published between January 2006 and February 2016 irrespective of study design – examining data from the last decade to reflect the period during which community-based testing has become more widespread and to maximise relevance to current practice.

Inclusion criteria for the review were studies which reported the proportion of individuals, detected with HIV through community-based testing, who link into HIV care and/or start ART, in SSA between January 2006 and February 2016 irrespective of study design. We excluded data on HIV testing in health-care facilities (HCFs) (or satellite sites of HCFs), or treatment initiation in the household, as our primary focus was on linkage to care to receive services (including ART initiation) at HCFs. We also excluded reports that pooled data from previously published studies to avoid duplication. Where there was substantial overlap of study subjects in more than one paper, we included the paper with the most complete information. Our search was limited to English language peer-reviewed journal articles; with no age restrictions for participants. We excluded conference abstracts.

Eligibility of articles was determined independently by two investigators (KS and OV). Using a standardised data-extraction form (KS and BH) independently extracted data on study characteristics and outcomes, with input from OV. Any disagreements were resolved by consensus. Markers of study quality were examined and strengths and limitations of the studies are presented in Table 2. Studies were not excluded for quality reasons using formal criteria for reporting scientific data, not least because a large proportion of the available data came from operational delivery of HTC services

and authors presented data as were available from the programmes. Data from randomised controlled trials are, however, emphasised in the Discussion section.

Ethical approval was not required as only published literature was included for review.

Data synthesis and analysis

If studies reported different approaches to testing (e.g. by study arm) we reported linkage outcomes by modality (e.g. M-HTS or HB-HTS) where possible. We calculated the proportion of individuals: i) linked-to-care and ii) initiated on ART and explored time to linkage to care and ART initiation. Further, we summarised retention on ART among those who initiated and extracted data on viral suppression, if studies reported this.

A meta-analysis was considered but upon review of the data, not deemed appropriate for the following reasons: i) variability in definitions used for numerators and denominators when calculating proportions linked-to-care and initiated ART; ii) variability between studies in follow-up time and approaches for measuring time for linkage to care and treatment initiation; iii) wide variability in findings.

5.4 Results

Characteristics of included studies

Our initial search yielded 2888 articles, of which 170 were reviewed as full-text articles and 20 were included in the final review (Supplementary Figure-1). From these 20 articles we present results of analyses based on 22 "studies" (Table-1) because one paper reported outcomes for HB- and M-HTS separately by modality, and a second reported results on random household HB-HTS and index TB patient household-member HB-HTS, as sub-groups. (9, 10) The studies were from six countries: Kenya, Lesotho, Malawi, South Africa, Swaziland, and Uganda (9-28), mostly from rural areas, and were conducted between 2008 and 2015. Most studies offered HTS for adults (mostly aged ≥18 years, but ≥13 years in one study), while 7 studies also offered HTS to children (mostly if they were orphaned or known to be HIV-exposed) (Supplementary Table-1). Regional adult HIV prevalence (obtained from UNAIDS national data if not reported by authors) ranged from 5-35%.

Twelve studies reported on linkage to care after HIV detection through HB-HTS – most were door-to-door services provided by lay counsellors; one was targeted HB-HTS for household contacts of TB patients(10); another was HB-HTS for randomly selected households(10); and one study used oral self-test kits which were distributed by trained volunteers from the community.(16) One of the door-to-door HB-HTS studies was from a national HIV testing campaign.(15) Eight studies were on M-HTS approaches – which included use of mobile-vans, tents in busy community locations, shopping areas,

transport hubs, etc. The two remaining studies presented linkage outcomes from HB- and M-HTS in combination without stratifying linkage to care and ART outcomes by the approach of the HTS.(26, 28) Three of the twenty-two studies provided HTS within a multi-disease intervention (one HB-HTS and two M-HTS studies).(9, 11)

Nine studies estimated population size served by the testing intervention and fourteen reported the number encountered and offered testing. Proportions offered testing among the population served by the HTS ranged from 19-98% (Supplementary Table-1). Proportions accepted testing among those offered testing ranged from 53% to ~100% in the twelve studies in which this could be calculated. The proportion accepting HIV testing of the population served by the HTS ranged from 17-91% (five home-based studies) while the only M-HTS study presenting the necessary data reported 25% coverage.

HIV-positivity among those tested ranged from 4-30% in HB-HTS studies; 5-15% in M-HTS studies (Table-1). In two studies which reported on both HB- and M-HTS in the same setting, HB-HTS had a slightly lower proportion detected with HIV than M-HTS (3.5% vs 4.7% and 3.6% vs 6.2%, respectively).(9, 28) Four studies excluded individuals who self-reported knowing they were HIV-positive but the majority included previously known HIV-positive individuals among the number reported as detected by HTS - therefore proportions HIV-positive from those studies are not limited to newly detected individuals.

As a result of losses from follow-up, data on proportions linked-to-care were limited to individuals who could be followed-up to identify linkage information (see Table-2). Twelve studies relied on individual self-report of linkage/ART initiation (three studies provided information on data which could be verified at clinics), eight studies used clinic records to obtain linkage and care outcomes, while two did not specify how outcomes were determined.

Linkage to care outcomes

Proportions linked-to-care

Definitions used for linkage to care varied as did methods of outcome ascertainment. Some studies described the outcome simply as “linkage to care” while others specified definitions used including proxy markers such as “CD4-count measured” or “CD4-count result received”; or identifying registration at the HCF where PLWH were referred (Table-1). Some studies restricted the denominator to newly diagnosed individuals when calculating proportions linked-to-care while others included those previously known to be HIV-positive provided they were not already in

care/on ART (Table-1). Seven studies did not report HIV-positive individuals as newly diagnosed or previously known PLWH and may have included individuals already in care.

Proportions linked-to-care ranged from 14-96% among HB-HTS studies and from 10-79% among M-HTS studies over 1-10 months of observation, with no obvious differences by HTS approach (Figure-1a). Labhardt et al compared outcomes after HB- and M-HTS in the same setting and found no difference in proportions linked-to-care (HB-HTS: 26% (10/39) vs M-HTS: 25% (19/75)). The data suggest (see Figure-1b) that linkage to care was higher when all PLWH not already on treatment (newly diagnosed and previously known HIV-positive) were examined, than among newly diagnosed PLWH alone.

Linkage to care by duration of follow-up

The periods of observation varied between studies and time available for observing linkage varied as a result. Studies ascertained linkage outcome by carrying out home-visits (occasionally in combination with telephone calls), once or at intervals after HTS; or consulted HCF records using a unique identifier to identify individuals who had been referred by HTS. The follow-up periods shown in Figure-2a represent the time between an individual being seen at HTS (when tested HIV-positive or self-reported HIV-positive status) and linkage-into-care. There was great variability in linkage to care between studies for similar time-points. The most commonly reported follow-up period for which linkage was reported was 3-months and proportions linked-to-care ranged from 7-85% (Figure-2a).

The total study periods are shown in Table-2. Few studies reported outcomes beyond 6-months following HTS (Figure-2a). Only two studies reported observed cumulative proportions linking-into-care over more than one time-point and while both showed progressive increases with time, the relative increase was small.(14, 27) Six studies are not shown in Figure-2a because they did not report time taken for individuals to link. Some of these studies described overall proportions linked-to-care at various periods of time following the HTS programme, but not the time interval between an individual's HIV detection at HTS and linkage to care. Six studies presented cumulative probability of linkage to care curves over time, using time-to-event analyses. Those estimates suggest that most linkage appears to occur in the first 3-months - with some studies showing incremental benefit up to 12-months,(14, 15, 27) while others showed plateauing over time after an initial steep increase in the first 1-3 months.(18, 19, 25)

Approaches to facilitate linkage to care

Several studies used field-worker follow-up as a means to encourage and monitor linkage to care. Follow-up visits to PLWH were employed by 7 HB-HTS studies and 1 M-HTS study (Table-1). One randomised controlled trial (RCT) with a factorial design (reporting linkage from HB- and M-HTs in combination), examined three approaches following detection of HIV - follow-up visits by a lay counsellor in one study arm and facilitation by a lay counsellor in the clinic in another study arm, both to enhance linkage to care, compared with a standard-of-care referral only arm.(26) Both approaches to improve linkage achieved high linkage to care with the clinic facilitation arm achieving a stronger effect than the lay counsellor home follow-up, when compared to the control (referral only) arm. Two studies used telephone calls to follow-up on PLWH detected through M-HTS.(20, 24) There is no clear evidence across all the studies that interventions to enhance linkage to care improved outcomes (Supplementary Figure-2a)

Eleven studies provided CD4-counts at the time of HTS (using portable point-of-care (POC) technology or providing results within days of HTS if venous sampling was done for laboratory testing) (Supplementary Table-1). There is no clear evidence across studies that the proportion linked-to-care was higher if CD4-counts were provided at the time of HIV detection (Figure-1c). The above factorial design RCT also randomly allocated the clients from the 3 study arms described earlier to have either POC CD4-countor CD4-count sampling in the clinic. They found no benefit from POC CD4-count sampling over clinic testing on linkage to care, ART initiation or viral suppression.(26)

Predictors of linkage to care

Several studies reported factors associated with linkage to care. In eight studies (3 HB-HTS,4 M-HTS, 1 combined HB-M-HTS) which reported on potential gender differences, five reported that fewer men linked-to-care than women(13-15, 17, 20) although one of those did not detect a statistically significant difference (17) and three other studies(11, 22, 28) found no association between gender and linkage to care. However, the trend was always for fewer men than women to link. Five studies found that older adults were more likely to link-to-care(13-15, 25, 28), while four observed no differences by age(11, 17, 22, 27). Parker et al was the only study to consider linkage in adolescents specifically (defined as 9-19 years), and while they observed that this group appeared to be more likely to link-to-care the association was of borderline statistical significance (adjusted odds ratio of 2.5 (95% confidence interval: 1.0-6.0)).(28) Several other studies included people as young as 13-years of age but considered them as adults. Three studies described the association of education with linkage to care, and no clear pattern was observed.(13, 14, 22) Marital status was also not predictive of linkage to care.(11, 13, 17, 22)

ART initiation outcomes

Proportions initiating ART

Proportions initiating ART among those eligible was reported in eight HB-HTS studies, two M-HTS studies and both combined HB-/M-HTS studies. As described above for linkage to care, the time available for ART initiation within the study periods varied (Table-2). The studies varied in ART eligibility criteria applied. Most studies had a CD4-count threshold of 350/cc^3, while several had a threshold of 200-250/cc^3 (Table-1). Ascertainment of CD4-count eligibility for ART was done at the time of HTS in some studies but only upon linkage to care and sampling at the clinic in other studies (Supplementary Table 1).

Reported proportions initiating ART ranged from 23-85% in HB-HTS and combined HB-/M-HTS studies. The wide range is in part explained by the fact that the denominators varied. Most studies used HIV-positive individuals identified as eligible as the denominator while a minority used either all individuals identified as HIV-positive or those linked-to-care, and not already on ART (irrespective of CD4-count) (Table-1). Further, as shown in Supplementary Table-1 some studies identified ART eligibility in the community at the time (or within days) of HTS, while in others eligibility was only assessed once individuals had linked-to-care. Both M-HTS studies had very small samples of PLWH (less than 20 individuals referred for ART) to assess initiation of ART (Table 1).(11, 22) There were no notable differences in ART initiation based on HTS approach (Figure-1d); newly diagnosed vs all PLWH not on treatment (new and previously diagnosed) (Supplementary Figure-2b); and whether CD4-count results were provided during HTS (Supplementary Figure-2c). Among PLWH who self-reported HIV-positive status after self-testing at home (and meeting ART eligibility criteria), 23% initiated ART.(16)

ART initiation by duration of follow-up

Eight studies reported ART initiation by time since HIV detection. There was no apparent trend and there was variability in the outcomes reported as seen in Figure-2b. Only two studies reported outcomes at more than one time-point, (14, 27) with one reporting cumulative outcomes based on time-to-event analysis estimates (27) (Figure-2b).

Predictors of ART initiation

Predictors of ART initiation were only examined in one study.(27) CD4-count was the only factor identified as predictive of ART initiation, with PLWH with CD4-counts <200/cc^3 more likely to initiate ART than those with CD4-counts of 201-350/cc^3. When we compared ART initiation by CD4-count

threshold across the studies in this review there were no distinct differences notable (data not shown).

Retention on ART and viral suppression

Retention on ART was reported by just one study. Macpherson et al reported that among those detected through self-testing at home, 6-months after ART initiation at the HCF, 76% (48/63) of participants were still on ART.(16) Three studies described viral suppression among participants on ART. One of them included patients who were already on ART before HB-HTS.(19) The remaining two studies both by Barnabas et al reported viral suppression (viral load < 1000 copies/ml) of 77% (59/77) among patients on ART for between 3-12 months in one study(27); and 85% (412/483) of patients who initiated ART within 9-months of HIV detection in another study (with variable durations on ART).(26)

5.5 Discussion

Community-level HIV testing has become established as a feasible and effective approach to increasing knowledge of HIV status in SSA(29). Others have published broad over-views of evidence following HTS (community and facility-based) and pooled outcomes, while acknowledging the limitations of summarising heterogeneous data.(5, 6) In our systematic review, we aimed to provide a more detailed scrutiny of the data on steps on the cascade of care - including examination of indicators used, measures of the numerators and denominators used to define linkage and treatment initiation, time-scales to observe outcomes etc. - with a specific focus on community-based HTS in SSA. We aimed to establish how effective community-level HTS approaches are at getting PLWH into care, beyond knowledge of HIV status alone, with a view to achieving 90-90-90 targets.

Definitions used for linkage to care and periods of observation for linkage to care and ART initiation outcomes varied between studies. Data were limited to individuals who could be traced and the proportion of those identified HIV-positive at HTS in whom linkage and ART initiation outcomes could be ascertained was often low (Supplementary Table-2). Most studies also relied on self-reported outcomes.

The above factors make summarising outcomes challenging and pooling of results potentially misleading. These important limitations in the data notwithstanding, we found that M-HTS and HB-HTS were equally effective at achieving LTC. We did not find discernible differences in terms of ART initiation although data on ART initiation after M-HTS was limited. There is a suggestion of higher linkage to care among those previously diagnosed (who had not already started ART) compared to

newly diagnosed individuals. This fits with the idea that individuals need time to act on an HIV-positive diagnosis. However, this group is heterogeneous and the barriers to link for those who have known their HIV status but not engaged with care compared to those already in care and have not started ART may be quite different.

As described, only one study performed a randomised comparison of interventions to enhance linkage and they reported nuanced findings.(26) While clinic facilitation by a lay counsellor was more effective than lay-counsellor home follow-up at increasing linkage to care, it is was the latter which was more effective at increasing uptake of ART (Table-1). There were also no differences in viral suppression at 9-months between PLWH randomised to intervention arms vs standard of care (referral for care only). This highlights the importance of measuring all the key steps of the cascade of care, as improvements in linkage to care may not translate to better treatment uptake or outcomes once on treatment. Providing CD4-count results at the time of community-based HTS did not appear to influence linkage to care or ART initiation in our systematic review. The difference between our findings and other data which have shown benefits following POC CD4-counts, is that we were looking at whether it benefited linkage to care following use in the community rather than use of POC CD4-counts in clinics for patients who had already attended.(30)

Studies reported that several patients were not initiated on ART (and told they were not eligible) despite being eligible.(28) (26) Transition to latest WHO guidelines of treatment for all PLWH will minimise decisions at the clinic level and reduce missed opportunities to offer/initiate treatment, provided that drugs are consistently available. Community delivery of ART for stable patients has to the potential to reduce the burden on HCFs and improve access for patients, thereby simplifying the cascade of care.(31) Macpherson et al examined home-initiation of ART following self-testing (in a randomised comparison with initiation of ART at the HCF which was included in this review).(16) They found higher proportions initiating ART in their home-initiation arm (although proportions retained on ART after 6 months were not different when compared with the facility-initiation arm).

Several studies on community-based HTS did not meet the eligibility criteria for inclusion in our review because data on linkage to care or ART initiation were not reported. This excluded some work-place or school-based HTS programmes and there is only one study on a national testing campaign. Among eligible studies several of them stopped at reporting proportions linked-to-care without describing proportions initiating ART, especially M-HTS studies. The scant reporting on viral suppression is probably related to low access to routine viral load testing in most SSA settings, but only one study included data on ART retention.

The under-reporting within studies of multiple steps on the cascade alludes to the challenges in obtaining accurate data at the individual-level, for the continuum of care. In addition, it may indicate that health-care provider/researchers lack the resources to examine and report HIV care as a continuum, instead targeting efforts at individual steps in isolation.

The limitations of this review have been described at length above. The strengths however include the fact that we limited our search to studies conducted in SSA over the last decade, thereby maximising relevance for current practice. The attention to detail when examining definitions used to measure outcomes also sheds light on the complexity of the data presented in current literature. We made the deliberate choice not to summarise data from studies in our review using meta-analysis, given the heterogeneity in the data. Further, we provide a template of proposed standard indicators as a guide for data collection and reporting of community-based HTS programme performance on the cascade of care (Supplementary Figure-3). While not exhaustive, we hope that this will help minimise inconsistencies in future literature.

The UNAIDS 90-90-90 targets are an important reminder of the multiple steps needed to provide comprehensive HIV care. With currently published data it was not possible to estimate current performance against 90-90-90 goals. The premise of the 90-90-90 targets is that the total number of PLWH in a given setting has to be known or, more realistically, estimated accurately and only then can the first proportion be calculated (to compare against the first-90). There is ambiguity in the term “sustained ART” (in the definition of the second-90) or what duration should be allowed for viral suppression to be achieved (to compare against the third-90). The other challenge is that the UNAIDS targets are “point” measures - at any point of time, 90% of HIV-positive individuals need to know their status, 90% of those who know their status need to be “on ART”, and 90% of the latter need to be virally suppressed. Data on time to link-to-care or initiate ART are therefore difficult to use to estimate the coverage against the UNAIDS targets, as they are not point measures.

This systematic review has identified the gaps and inconsistencies in the current literature quantifying the continuum of care. We found no differences in linkage to care or ART initiation by community testing approach but comparisons were hampered by the variability in reporting. We recommend that standardised measures of reporting of steps of the cascade of care are much needed in order to be able to measure progress against targets and across settings.

Conflicts of interests

We have no conflicts of interests to declare.

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Authors' contributions

KS led on developing the research goals and aims, data extraction and analysis, and writing the paper. BH was the second reviewer extracting and analysing data. OV was the second reviewer performing the literature search and contributed to extraction of data. RH provided guidance and over-sight of the content. All authors commented on the paper, and read and approved the final version.

5.6 References

1. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. http://wwwunaidsorg/sites/default/files/media_asset/90-90-90_en_0pdf. 2014;Accessed on 30th July 2016.
2. Cohen M, Chen Y, M. M. Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Vancouver. 2015;Oral Presentation(Abstract MOAC0101LB).
3. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The New England journal of medicine. 2015;373(9):795-807.
4. TEMPRANO ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.
5. Sharma M, Ying R, Tarr G, Barnabas R. Systematic review and meta-analysis of community and facility-based HIV testing to address linkage to care gaps in sub-Saharan Africa. Nature. 2015;528(7580):S77-85.
6. Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med. 2013;10(8):e1001496.
7. Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N. Uptake of Home-Based Voluntary HIV Testing in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. PLoS Med. 2012;9(12):e1001351.
8. UNAIDS. 90-90-90: On the right track towards the global target. 2016;Accessed on 30th July 2016.
9. Labhardt ND, Motlomelo M, Cerutti B, Pfeiffer K, Kamele M, Hobbins MA, et al. Home-based versus mobile clinic HIV testing and counseling in rural Lesotho: a cluster-randomized trial. PLoS Med. 2014;11(12):e1001768. doi: 10.1371/journal.pmed..
10. Shapiro AE, Variava E, Rakgokong MH, Moodley N, Luke B, Salimi S, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. American journal of respiratory and critical care medicine. 2012;185(10):1110-6.
11. Chamie G, Kwarisiima D, Clark TD, Kabami J, Jain V, Geng E, et al. Uptake of community-based HIV testing during a multi-disease health campaign in rural Uganda. PLoS One. 2014;9(1):e84317. doi: 10.1371/journal.pone.0084317. eCollection 2014.
12. Dalal W, Feikin DR, Amolloh M, Ransom R, Burke H, Lugalia F, et al. Home-based HIV testing and counseling in rural and urban Kenyan communities. J Acquir Immune Defic Syndr. 2013;62(2):e47-54. doi: 10.1097/QAI.0b013e318276bea0.
13. Genberg BL, Naanyu V, Wachira J, Hogan JW, Sang E, Nyambura M, et al. Linkage to and engagement in HIV care in western Kenya: an observational study using population-based estimates from home-based counselling and testing. Lancet HIV. 2015;2(1):e20-6.
14. Hatcher AM, Turan JM, Leslie HH, Kanya LW, Kwena Z, Johnson MO, et al. Predictors of linkage to care following community-based HIV counseling and testing in rural Kenya. AIDS Behav. 2012;16(5):1295-307. doi: 10.007/s10461-011-0065-1.
15. MacKellar DA, Williams D, Storer N, Okello V, Azih C, Drummond J, et al. Enrollment in HIV Care Two Years after HIV Diagnosis in the Kingdom of Swaziland: An Evaluation of a National Program of New Linkage Procedures. PLoS One. 2016;11(2):e0150086.
16. MacPherson P, Lalloo DG, Webb EL, Maheswaran H, Choko AT, Makombe SD, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: a randomized clinical trial. JAMA. 2014;312(4):372-9. doi: 10.1001/jama.2014.6493.
17. Medley A, Ackers M, Amolloh M, Owuor P, Muttai H, Audi B, et al. Early uptake of HIV clinical care after testing HIV-positive during home-based testing and counseling in western Kenya. AIDS Behav. 2013;17(1):224-34. doi: 10.1007/s10461-012-0344-5.

18. Tumwebaze H, Tumwesigye E, Baeten JM, Kurth AE, Revall J, Murnane PM, et al. Household-based HIV counseling and testing as a platform for referral to HIV care and medical male circumcision in Uganda: a pilot evaluation. PLoS One. 2012;7(12):e51620. doi: 10.1371/journal.pone.0051620. Epub 2012 Dec 13.
19. van Rooyen H, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2013;64(1):e1-8. doi: 10.1097/QAI.0b013e31829b567d.
20. van Zyl MA, Brown LL, Pahl K. Using a call center to encourage linkage to care following mobile HIV counseling and testing. AIDS care. 2015;27(7):921-5.
21. Bassett IV, Regan S, Luthuli P, Mbonambi H, Bearnot B, Pendleton A, et al. Linkage to care following community-based mobile HIV testing compared with clinic-based testing in Umlazi Township, Durban, South Africa. HIV Med. 2014;15(6):367-72. doi: 10.1111/hiv.12115. Epub 2013 Nov 19.
22. Govindasamy D, Kranzer K, van Schaik N, Noubary F, Wood R, Walensky RP, et al. Linkage to HIV, TB and non-communicable disease care from a mobile testing unit in Cape Town, South Africa. PLoS One. 2013;8(11):e80017. doi: 10.1371/journal.pone.0080017. eCollection 2013.
23. Kranzer K, Govindasamy D, van Schaik N, Thebus E, Davies N, Zimmermann M, et al. Incentivized recruitment of a population sample to a mobile HIV testing service increases the yield of newly diagnosed cases, including those in need of antiretroviral therapy. HIV Med. 2012;13(2):132-7.
24. Larson BA, Schnippel K, Ndibongo B, Xulu T, Brennan A, Long L, et al. Rapid point-of-care CD4 testing at mobile HIV testing sites to increase linkage to care: an evaluation of a pilot program in South Africa. J Acquir Immune Defic Syndr. 2012;61(2):e13-7.
25. Naik R, Doherty T, Jackson D, Tabana H, Swanevelder S, Thea DM, et al. Linkage to care following a home-based HIV counselling and testing intervention in rural South Africa. Journal of the International AIDS Society. 2015;18(1).
26. Barnabas R, van Rooyen H, Tumwisigye E, Brantley J, Baeten J, van Heerden A, et al. Uptake of antiretroviral therapy and male circumcision after community-based HIV testing and strategies for linkage to care versus standard clinic referral: a multisite, open-label, randomised controlled trial in South Africa and Uganda. Lancet HIV. 2016;Accessed on 10th March 2016.
27. Barnabas RV, van Rooyen H, Tumwesigye E, Murnane PM, Baeten JM, Humphries H, et al. Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: A prospective, observational intervention study. The Lancet HIV. 2014;1(2):e68-e76.
28. Parker LA, Jobanputra K, Rusike L, Mazibuko S, Okello V, Kerschberger B, et al. Feasibility and effectiveness of two community-based HIV testing models in rural Swaziland. Trop Med Int Health. 2015;20(7):893-902. doi: 10.1111/tmi.12501. Epub 2015 Apr 2.
29. World Health Organization. Consolidated Guidelines on HIV Testing Services. http://appswhoint/iris/bitstream/10665/179870/1/9789241508926_engpdf?ua=1&ua=1. 2015;Accessed on 30th July 2016.
30. Vojnov L, Markby J, Boeke C, Harris L, Ford N, Peter T. POC CD4 Testing Improves Linkage to HIV Care and Timeliness of ART Initiation in a Public Health Approach: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(5):e0155256.
31. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, van Cutsem G, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Trop Med Int Health. 2014;19(8):968-77.

Table 5.1: Study characteristics

Author, Year	Country, Rural/ Urban	Testing approach	Intervention(s) to enhance LTC[1]	Proportion HIV+ (%)	Number HIV+		Numerator for % LTC	Denominator for % LTC	Proportion LTC % (n/N)	Numerator for % initiated ART	Denominator for % initiated ART	Proportion initiated ART % (n/N)
					Newly identified HIV+	Known HIV+, not in care/ on ART						
HB-HTS												
Barnabas, 2014[2]	South Africa & Uganda, Rural & peri-urban	Door-to-door HB-HTS study	i, ii &iii	19.0	229	152	n visiting an HIV clinic	N newly diagnosed or known HIV+ not on ART	96% (367/381)	n initiated ART	N newly diagnosed or known HIV+ not on ART & CD4 <350/cc[3]	76% (94/123)
Dalal, 2013	Kenya, Rural + urban	Door-to-door HB-HTS implementation	ii & iii	16.3	1839	NR	n accessing patient support centre	N newly diagnosed	47% (454/958)	n initiated ART	N newly diagnosed adults & CD4 <250/cc[3]	34% 43/125
Genberg, 2015	Kenya, Rural,	Door-to-door HB-HTS implementation	iv	11.0	1360	344	n having clinical encounter with HIV care provider	N newly diagnosed or known HIV+ not in care	14% (243/1704)	n initiated ART	N newly diagnosed, eligible and LTC (ART eligibility NR)	85% (78/92)
											N known HIV+ not on ART (ART eligibility NR)	53% (18/34)
Labhardt, 2014	Lesotho, Rural	Door-to-door HB-HTS and multi-disease services (within a cluster randomised trial)	v	3.6	39	NR	n linked to care	N newly diagnosed	26% (10/39)	NR	NR	NR
MacKellar, 2016	Swaziland, Rural + urban	Door-to-door HB-HTS national campaign	ii & vi	NR	850	NR	n received CD4 count result or WHO staged	N newly diagnosed	27% (209/788)	NR	NR	NR
Medley, 2013	Kenya, Rural	Door-to-door HTS within demographic surveillance	ii & iii	11.0	923	NR	n currently attending to HIV clinical care	N adults tested HIV+	42% (312/737)	n on ART	N adults tested HIV+ and LTC (ART eligibility NR)	26% (80/312)

Author, Year	Country, Rural/ Urban	Testing approach	Intervention(s) to enhance LTC[1]	Proportion HIV+ (%)	Number HIV+		Numerator for % LTC	Denominator for % LTC	Proportion LTC % (n/N)	Numerator for % initiated ART	Denominator for % initiated ART	Proportion initiated ART % (n/N)
					Newly identified HIV+	Known HIV+, not in care/ on ART						
Naik, 2015	South Africa, Rural	Door-to-door HB-HTS study	ii	9.7	274	NR	n linked to care	N clients tested HIV+ not already in pre-ART or ART care	76% (273/359)	NR	NR	NR
Tumwebaze, 2012[2]	Uganda, Rural & peri-urban	Door-to-door HB-HTS study	i & ii	9.8	77	36	n visiting an HIV clinic	N newly diagnosed or known HIV+ but not on ART	85% (96/113)	n initiated ART	N newly diagnosed or known HIV-positive not on ART & CD4 <250/ cc^3	71% (15/21)
van Rooyen, 2014	South Africa, Rural	Door-to-door HB-HTS study	i & iii	30.0	73	64	n visited HIV clinic	N adults newly diagnosed or known HIV+ but not on ART	96% (131/137)	n initiated ART	N newly diagnosed &CD4 <350/cc^3 and LTC	54% (19/35)
											N known HIV+, not on ART & CD4 <350/cc^3 and LTC	65% (17/26)
MacPherson, 2014	Malawi, Urban	Study involving self-testing with oral test kits offered to household members (within a cluster randomised trial)	v	NR	278	NR	NR	NR	NR	n initiated ART	N reporting HIV+ self-test result & CD4 <350/cc^3 and LTC	23% (63/376)
Shapiro, 2012	South Africa, urban	Index case (TB patients) driven HB-HTS study	ii for ART eligible/ iv for ART non-eligible)	14.6	NR	NR	NR	NR	NR	n initiated ART	N HIV+ household contacts of a TB index case & CD4 <250/cc^3	41% (13/32)

Author, Year	Country, Rural/ Urban	Testing approach	Intervention(s) to enhance LTC[1]	Proportion HIV+ (%)	Number HIV+		Numerator for % LTC	Denominator for % LTC	Proportion LTC % (n/N)	Numerator for % initiated ART	Denominator for % initiated ART	Proportion initiated ART % (n/N)
					Newly identified HIV+	Known HIV+, not in care/ on ART						
Shapiro, 2012	South Africa, urban	Randomly selected household HB-HTS study	As above	10.6	NR	NR	NR	NR	NR	n initiated ART	N HIV+ non-contact participants with CD4 <250/cc[3]	53% (10/19)
Community outreach and HB-HTS												
Barnabas, 2016	South Africa & Uganda, Rural	Door-to-door HB-HTS & M-HTS using mobile testing (details NR) (LTC assessed within factorial design randomised controlled trial[4])	vii	15.0	992	333	n visiting an HIV clinic	N newly diagnosed & known HIV+ not on ART (Lay counsellor FU arm)	93% (419/449)	n initiated ART	N newly diagnosed & known HIV+ not on ART (Lay counsellor FU arm)	41% (185/449)
								N newly diagnosed & known HIV+ not on ART (Clinic facilitation arm)	98% (421/431)		N newly diagnosed & known HIV+ not on ART (Clinic facilitation arm)	37% (161/431)
								N newly diagnosed & known HIV+ not on ART (Referral only arm)	89% (378/423)		N newly diagnosed & known HIV+ not on ART (Referral only arm)	34% (142/423)
Parker, 2015	Swaziland, Rural	Door-to-door HB-HTS implementation	ii & vi	3.8	242	12	n registered in pre-ART care	N newly diagnosed	34% (135/398)	n initiated ART	N newly diagnosed & CD4 <350/cc[3] and LTC	52% (22/42)
		M-HTS with tents at community locations	As above	4.7	96	12						

Author, Year	Country, Rural/ Urban	Testing approach	Intervention(s) to enhance LTC[1]	Proportion HIV+ (%)	Number HIV+		Numerator for % LTC	Denominator for % LTC	Proportion LTC % (n/N)	Numerator for % initiated ART	Denominator for % initiated ART	Proportion initiated ART % (n/N)
					Newly identified HIV+	Known HIV+, not in care/ on ART						
Community outreach												
Bassett, 2015	South Africa, Urban	M-HTS with mobile units at taxi stands, markets, and sporting grounds	Phlebotomy for CD4-count done at time of M-HTS; v for clients who retrieved results	10.0	455	455	n retrieved CD4-count (within 90 days) *OR* initiated ART literacy (at any time)	N newly diagnosed	10% (45/455)	NR	NR	NR
Chamie, 2012	Uganda, Rural	M-HTS multi-disease campaign held at community locations	i & iv	7.8	82	28	n attending at least one clinic appointment	N newly diagnosed	34% (25/64)	n initiated ART	N newly diagnosed & CD4 ≤100/cc^3 and LTC	83% (5/6)
Govindasamy, 2013	South Africa, Urban & peri-urban	M-HTS provided five days per week at work sites (i.e. farms), outside various community locations	i & ii	5.5	294	NR	n attended HCF within ≤1mth if CD4≤200/cc^3; ≤3mth if CD4 201-350/cc^3; ≤6mth if CD4>350/cc^3	N newly diagnosed CD4≤200/cc^3	38% (18/48) CD4 200/cc^3	n on ART at 1mth follow-up	N newly diagnosed adults & CD4 ≤200/cc^{3}and LTC	83% (15/18)
								N newly diagnosed CD4 201-350/cc^3	53% (44/83) CD4 201-350/cc^3			
								N newly diagnosed & CD4>350/cc^3	53% (77/145)			
Hatcher, 2012	Kenya, Urban	M-HTS using tents in six community sites	i & v	NR	808	NR	n linked to care	N tested HIV+ and not in HIV care	10m: 81% (393/483)	NR	NR	NR

Author, Year	Country, Rural/ Urban	Testing approach	Intervention(s) to enhance LTC[1]	Proportion HIV+ (%)	Number HIV+		Numerator for % LTC	Denominator for % LTC	Proportion LTC % (n/N)	Numerator for % initiated ART	Denominator for % initiated ART	Proportion initiated ART % (n/N)
					Newly identified HIV+	Known HIV+, not in care/ on ART						
Kranzer, 2012[2]	South Africa, Urban	M-HTS using a van parked at a township shopping centre or in front of a primary school	iii or vi if CD4 <350/cc[3]	10.9	102	NR	n linked to care	N newly diagnosed & CD4 ≤350/cc[3]	79% (26/33)	NR	NR	NR
Labhardt, 2014	Lesotho, Rural	Community gatherings in villages followed by M-HTS and multi-disease services (within a cluster randomised trial)	v	7.5	75	NR	n linked to care	N newly diagnosed	25% (19/75)	NR	NR	NR
Larson, 2012	South Africa, NR	M-HTS using mobile units and tents/gazebos in taxi ranks/ shopping malls	i (if nurse providing M-HTS had equipment), v & vi	NR	NR	NR	n completed referral visit	N tested HIV+	54% (172/316)	NR	NR	NR
van Zyl, 2015	South Africa Rural + urban	M-HTS (details NR)	vi	NR	NR	NR	n tested HIV+ and ART eligibility assessed.	N tested HIV+	51% (563/1096)	NR	NR	NR

1. i:POC CD4; ii: Written referral; iii: Lay counsellor follow-up (FU); iv: Verbal referral; v: Referred but mode of referral not reported; vi: Telephone reminder or call to FU; vii: Randomised comparison of POC CD4-count vs clinic CD4-count + Randomised comparison of lay counsellor FU vs lay counsellor clinic facilitation vs referral only (mode of referral not reported)
   If follow-up (FU) visits were done, frequency of and intervals between FU are shown in Supplementary Table 1
2. Incentives provided for study participation (not for linkage-to-care)
3. Children whose biological mother was deceased or known to be HIV+
4. We have not shown outcomes by POC CD4-count vs clinic CD4-count arms as outcomes were very similar

Table 5.2: Markers of study quality and additional characteristics

Author, Year	How was outcome determined?	Did outcome exclude those already LTC (or on ART)?	Period of Study for LTC (or ART initiation)	% in whom outcome *not* ascertained among those testing HIV+	Reasons outcome not ascertained	Who delivered HTS?	Timing of interim follow-up visits	Participant selection
HBHTS								
Barnabas, 2014	Self-reported & review of clinic cards/medications with the individual	Y (excluded individuals on ART)	12m	10% (n=60/635)[i]	Moved (57%; n=34) Died (25%; n=15) Withdrew (18%; n=11)	Lay counsellor	1, 3, 6, 9m with voice and/or text message reminders of follow-up visits	Individuals consenting to door-to-door offer of HBHTS
Dalal, 2013	Self-reported	Y	1m	48% (n=881/1839)	NR	Trained counsellors	1m post-HTS	Individuals consenting to a household visit from HBHTS & accepting an offer of HBHTS
Genberg, 2015	Health facility records	Y	3m	2% (n=33/1360)	LTFU (91%; n=30) Died (9%; n=3)	Trained counsellors	NR	Individuals consenting to door-to-door offer of HBHTS
Labhardt, 2014 (HBHTS)	Health facility records	N	1m	0	NA	Lay counsellor and nurse	No FU visits	Individuals consenting to door-to-door HBHTS
MacKellar, 2016	Health facility records	Y	26m	NR[ii]	NR	NR	FU by telephone at 8w	Individuals consenting to door-to-door offer of HBHTS
Medley, 2013	Self-reported	N	2-4m post-HBHTS	32% (n=350/1087)	Did not consent to FU visits (41%; n=144) Migrated (25%; n=89); Refused (20%; n=70); Died (6%; n=20); Missing/not at home (8%; n=27)	Trained counsellors	3 attempts to visit home by HIV-positive peer educators	Individuals consenting to door-to-door offer of HBHTS
Naik, 2015	Self-reported & health facility records	Y	3m	18% (n=79/438)	LTFU completely or LTFU prior to 3mth (90%; n=71) Died (10%; n=8)	Lay counsellors	"Periodic" home visits or phone calls	Individuals consenting to door-to-door offer of HBHTS
Tumwebaze, 2012	Self-reported	N	3m	2% (n=3/152)	NR	Trained HBHTS study staff	1 & 2m	Individuals consenting to door-to-door offer of HBHTS

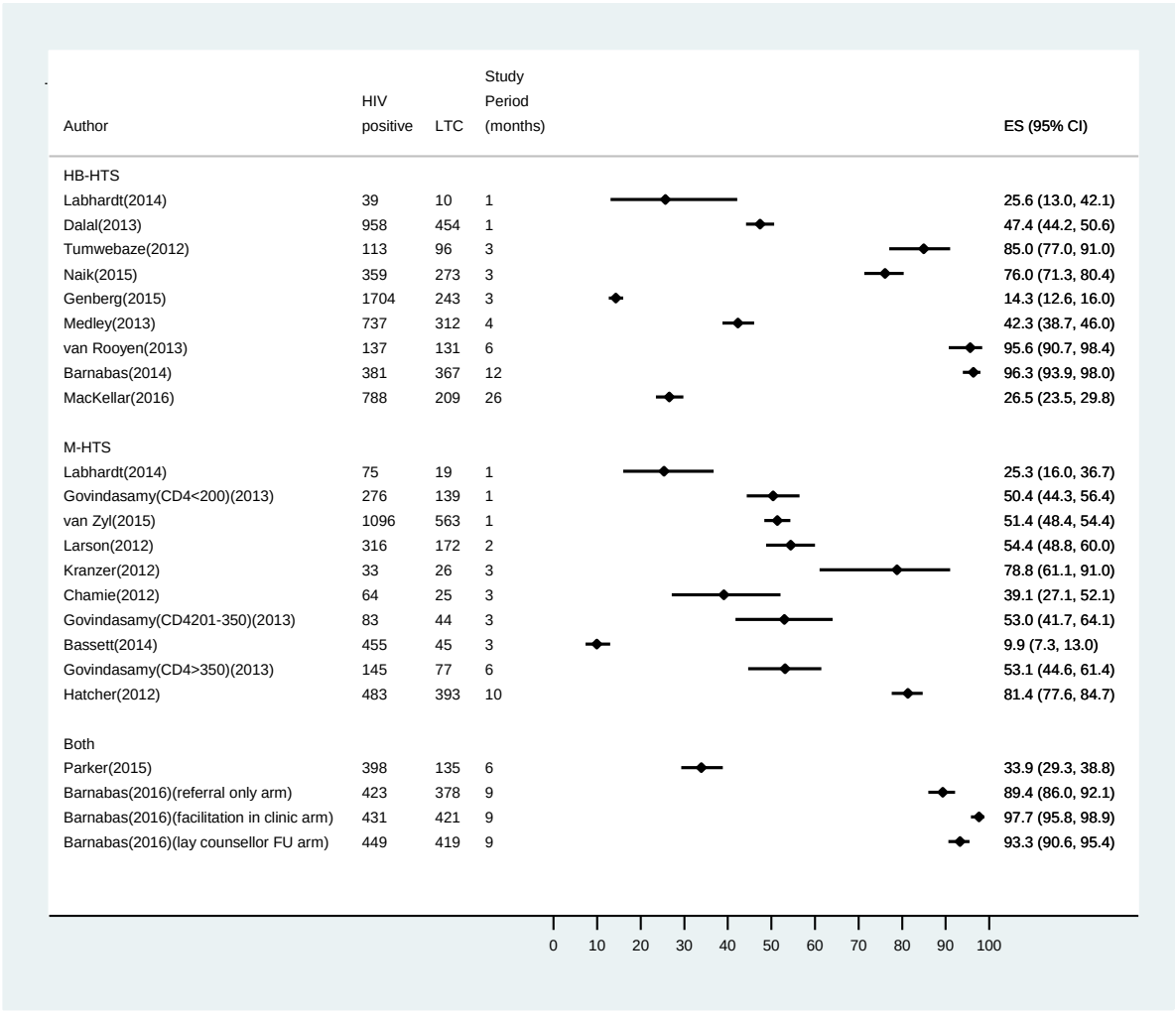
van Rooyen, 2013	Self-reported & review of care documentation / medication with individual	N	6m	4% (n=5/137)	Died (60%; n=3) Withdrew (40%; n=2)	Lay counsellors or nurse assistants	1, 3, & 6m	Individuals consenting to door-to-door offer of HBHTS
MacPherson, 2014	Health facility records	Y (restricted to those not initiated on ART)	6m (ART initiation)	NA	NA	Self-testing	No FU visits	Individuals opting to self-test (mostly at home)
Shapiro (TB-contacts), 2012	NR	N	2m (ART initiation)	NR	NR	Nurse & lay counsellors	NR	HBHTS offered to household members of index TB patient
Shapiro (Random HH), 2012	NR	N	2m (ART initiation)	NR	NR	Nurse & lay counsellors	NR	HBHTS offered to household members of randomly selected households
Community outreach & HBHTS								
Barnabas, 2016	Self-reported & review of clinic cards/medications with individual	Y (excluded individuals on ART)	9m	3% (n=40/1325)[iii]	Died (34%; n=8) Moved (18%; n=6) Withdrew (9%; n=3) Unknown (68%; n=23)	Lay counsellors (Uganda); Lay counsellors & nurse teams (SA)	1,3 and 6m for individuals randomised to lay counsellor FU	Individuals consenting to door-to-door offer of HBHTS or self-selected through MHTS
Parker, 2015 (HBHTS)	Health facility records	N	6m	NR	NR	HTS counsellors	NR	Self-selection through MHTS
Parker, 2015 (MHTS)								Individuals consenting to door-to-door HBHTS
Community outreach								
Bassett, 2014	Health facility records	Y	3m	NR	NR	Trained counsellors	No FU visits	Self-selection through MHTS
Chamie, 2012	NR	Y	3m	22% (n=18/82)	Implementation errors (72%; n=13)	Trained counsellors	NR	Self-selection through MHTS
Govinda-samy, 2013	Self-reported	Y	Dependent on CD4 cell count – up to 6m	6% (n=18/294)	Refused (n=4; 22%) Followed-up before follow-up period (n=14; 78%)	Nurse & counsellor supported	Telephone call 1w post-diagnosis	Self-selection into mobile HTS

Hatcher, 2012	Self-reported	Y	10m	40% (n=325/808)	Did not provide locator information (38%; n=124) Not located at 10m FU (42%; n=137) Did not consent to FU interview (15%; n=47) Reported that they already enrolled in care prior to MHTS (5%; n=17)	Trained counsellors	FU visits conducted but timing NR	Self-selection through MHTS
Labhardt, 2014 (MHTS)	Health facility records	N	1m	0	NA	Lay counsellor and nurse	No FU visits	Self-selection through MHTS
Kranzer, 2012	Self-reported	Y	1 & 3m (dependent on CD4 cell count at diagnosis)	20% (n=8/41) (restricted to those with CD≤350)	Unable to contact by telephone or home visits (100%; n=8)	Nurse with counsellor support (who conducted HTS NR)	Up to 7 attempts to contact (phone or face-to-face) individuals with CD4 ≤200 at 4w & CD201-350 at 12w post-HTS	Individuals accepting an invitation to MHTS
Larson, 2012	Self-reported	N	2m	38% (n=192/508)	Could not be contacted by telephone (100%; n=192)	Nurse	Three attempts to contact individuals by phone 8w post-HTS	Self-selection through MHTS
van Zyl, 2015	Self-reported	N	1m	NA[iv]	NA	NR	Daily FU telephone calls	Self-selection through MHTS

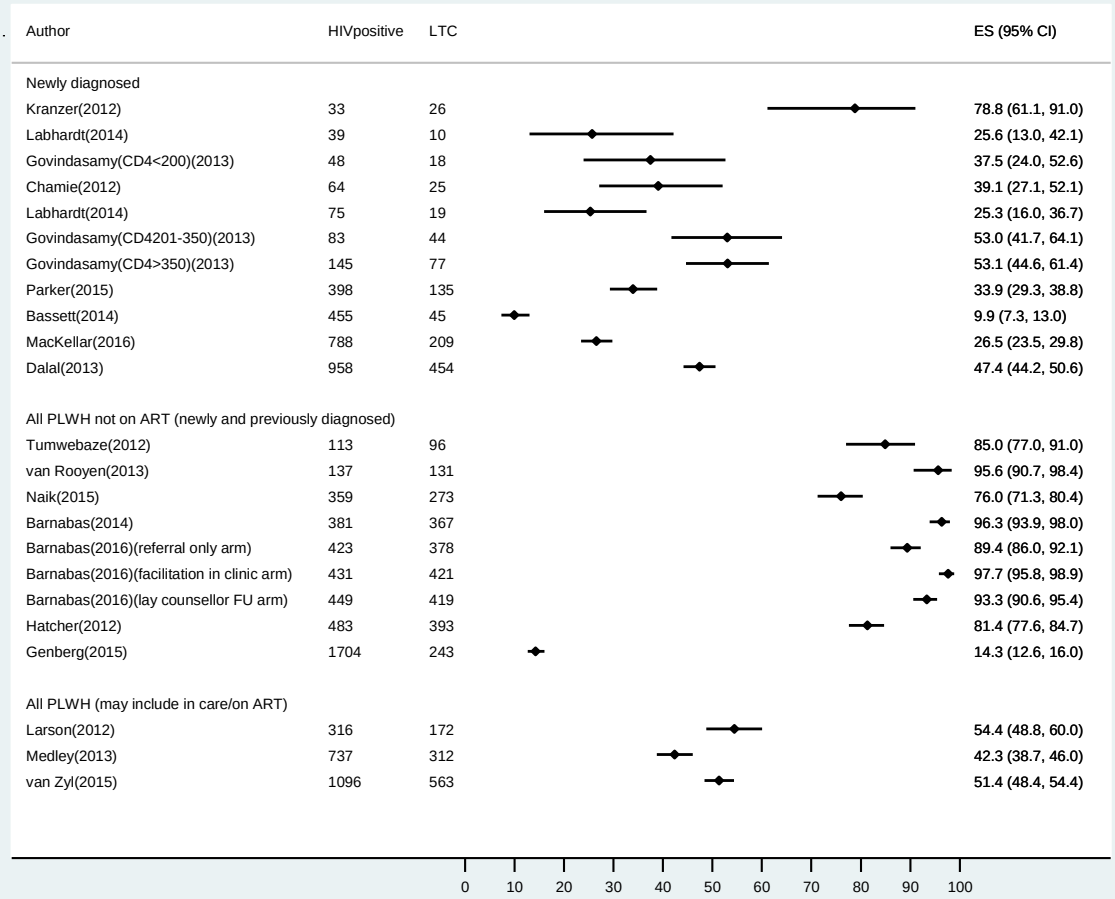
1. By 12m FU, LTFU reported among all individuals, including individuals on ART. Denominator therefore includes N=254 known HIV+ & on ART
2. Not reported (NR) as outcome not reported separately for those detected through HB-HTS
3. Loss to follow-up is reported as individuals not followed-up at 9m; some of these individuals contributed to analysis of LTC and/or ART prior to being LTFU
4. Not applicable (NA): Individuals defined as "not linked to care" regardless of whether or not the individual was contactable. Among individuals not LTC, reasons available for LTC N=442: Asked not to be called (14%; n=63); Deceased (0.2%; n=1); Called many times (56%; n=249) Incorrect information (18%; n=79); No telephone (11%; n=50)

Figure 5.1: Forest plots showing LTC outcomes by (a) HTS approach; (b) by PLWH sub-groups; (c) by when CD4-count result was available; and (d) ART initiation outcomes by HTS approach

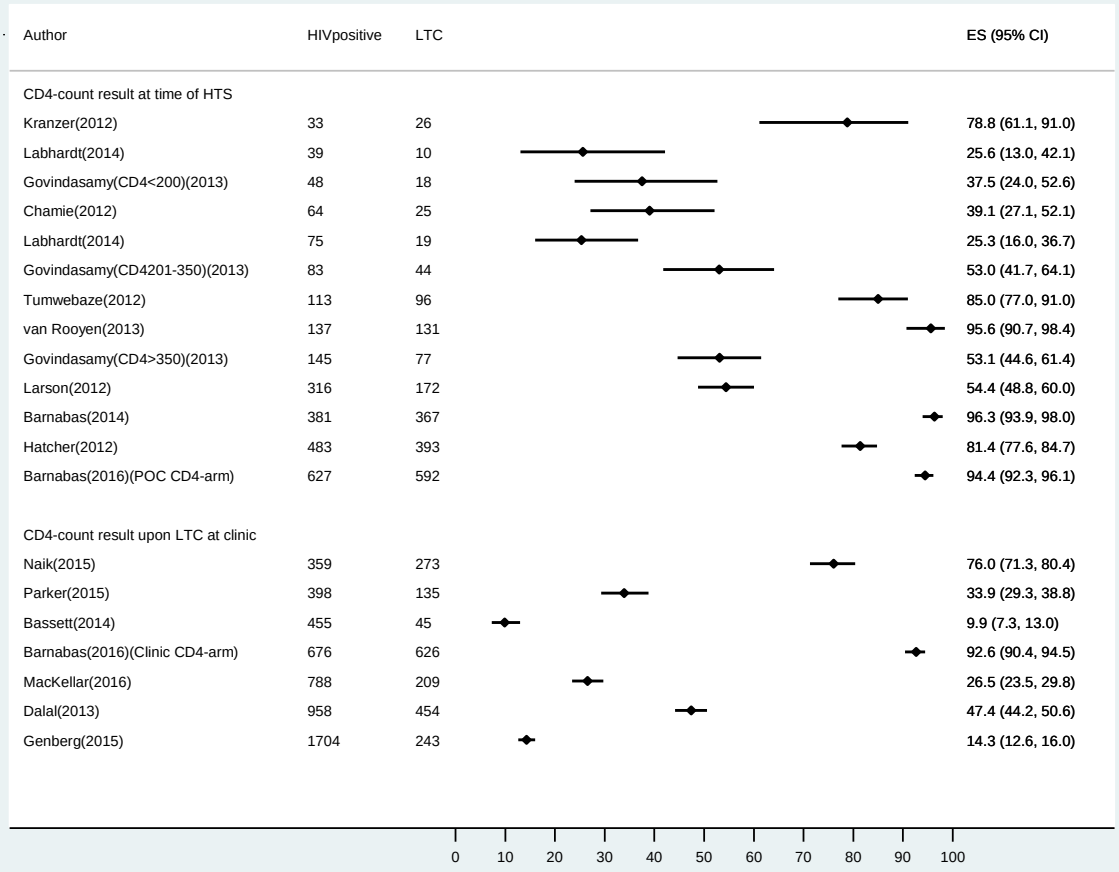
(a) Proportions linked-to-care (LTC) by HTS approach



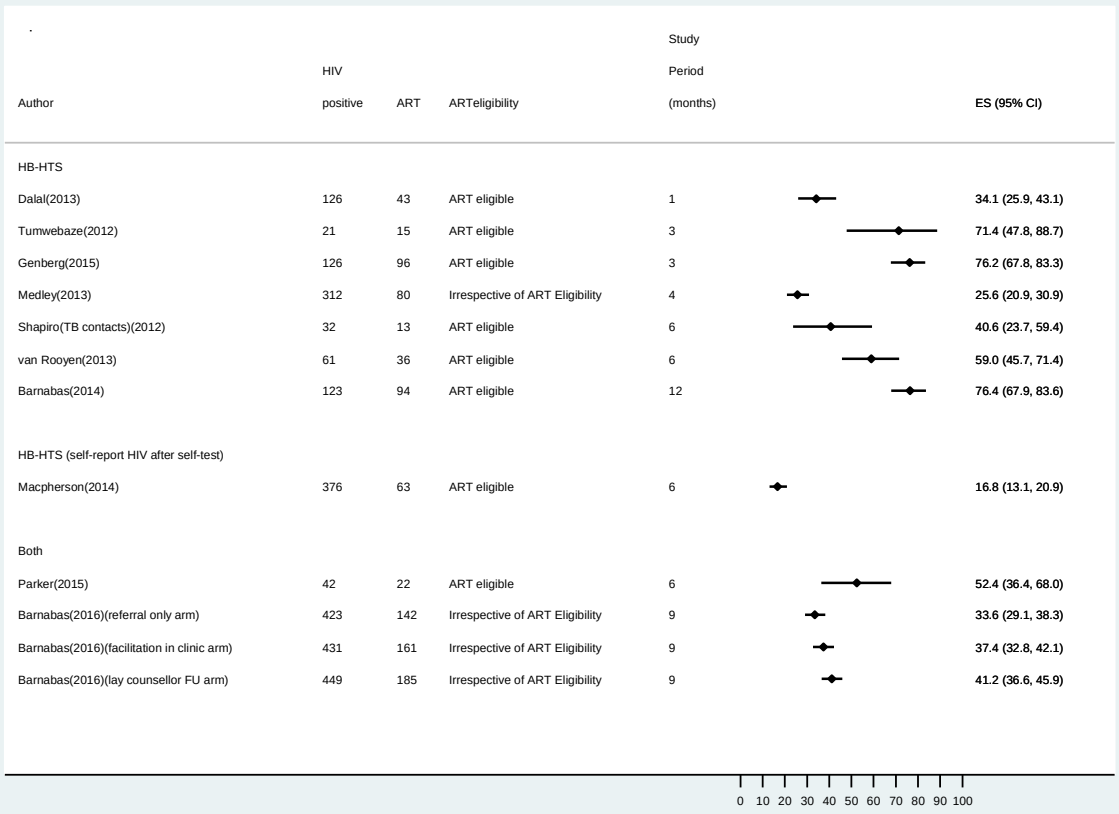
(b) Proportions LTC by PLWH sub-groups



(c) Proportions LTC by when CD4-count result was available



(d) Proportions initiating ART by HTS approach



*Three studies (Shapiro (Random HH), 2012 (HB-HTS study); Govindasamy, 2013 & Chamie, 2012 (both M-HTS studies)) with less than 20 in the denominator (HIV positive) are not shown above

Figure 5.2a-b: Time taken following HIV-detection at HTS for individuals – (a) to link-to-care, (b) to initiate ART

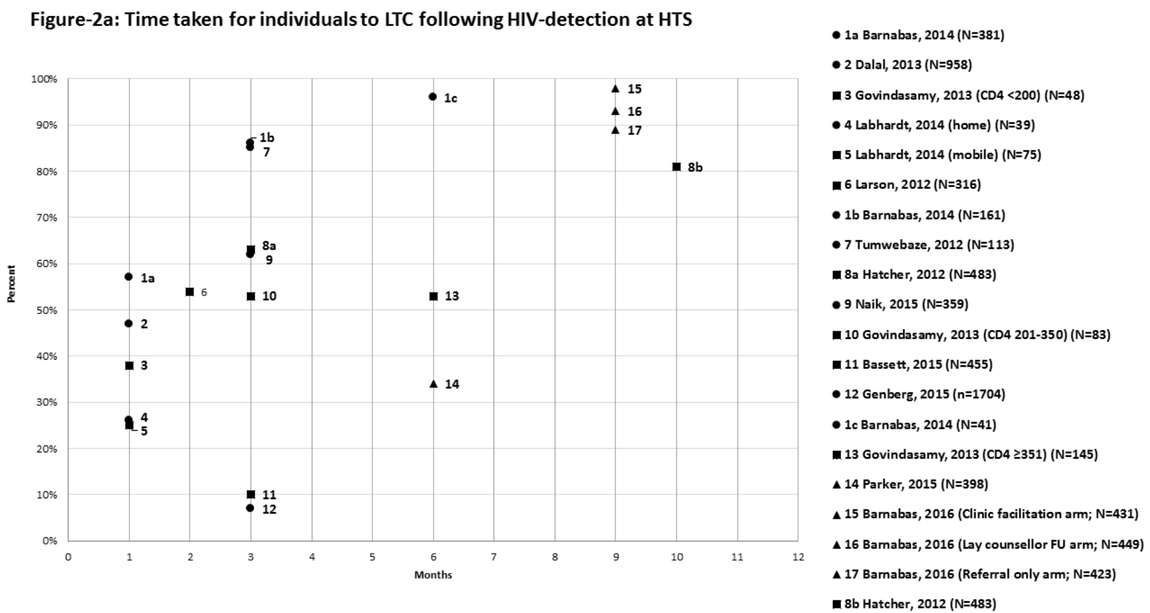
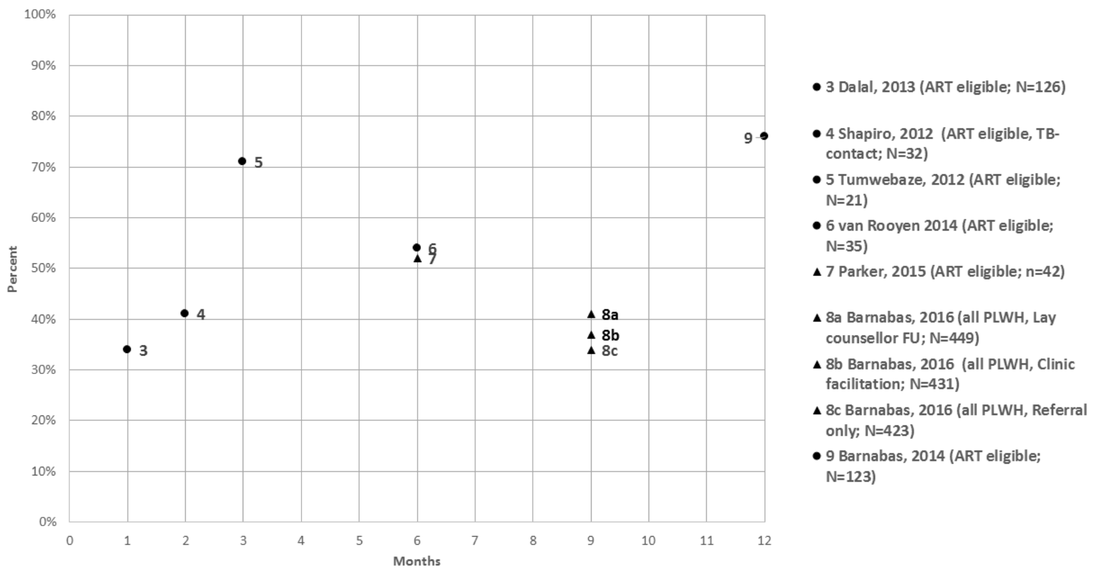


Figure-2b: Time taken for individuals to initiate ART following HIV-detection at HTS



Supplementary Table 5.1: Additional study information

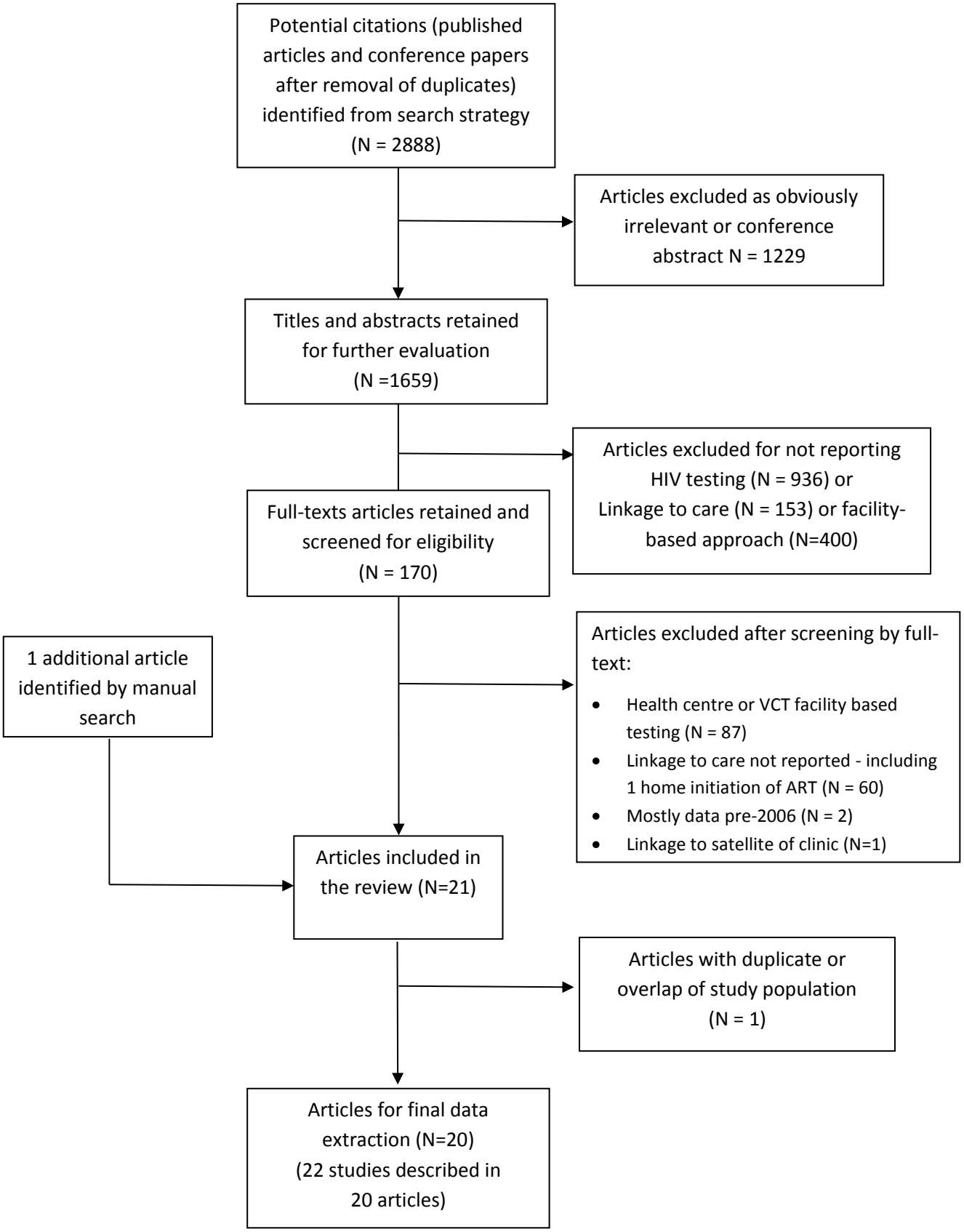
Author, Year	Primary objective	Estimated population eligible for testing intervention	Number offered testing (%) [1]	Number accepted testing (%) [2]	Adults or children offered HTC	% of individuals accepting HTS that are male [3]	Median CD4-count measured at diagnosis /cc³ (IQR)	Median CD4-count measured at LTC /cc³ (IQR)	CD4-count result available when 1. HIV detected (or within days) 2. after LTC
HB-HTS									
Barnabas, 2014	To assess linkage to local HIV clinics, ART initiation among individuals eligible by national guidelines and viral suppression at 12mths	NR	3545	3393 (96%)	Adults aged ≥18y	42% (n=1424/3393)	456 (288-628)	NR	1
Dalal, 2013	To assess acceptance of HB-HTS, HIV prevalence and treatment referral rates	NR	24450	19966 (82%)	Adults & children[4]	45% (n=8889/19966)	403 (252–594)	NR	2
Genberg, 2015	Proportion with known HIV infection identified at HB-HTS who had ever engaged in care; time to and predictors of linkage to care (LTC)	66723 (Including children – ineligible in this study)	32333 Adults (≥13y)	32269 (~100%)	Adults (≥13y)	NR	NR	436 (267-558)	2
Labhardt, 2014 (HB-HTS)	To compare HTS uptake, HIV prevalence and LTC within 1mth between HB-HTS and M-HTS	6311	1171 (19%)	1083 (92%)	Adults & children	Men (≥12yrs): 30% (n=247/812)	438 (265-650)	NR	1
MacKellar, 2016	To evaluate compliance with new national linkage and retention standard operational procedures and enrolment in HIV care	NR	NR	NR	Adults	NR	NR	280 (165–420)	2
Medley, 2013	To describe HB-HTS coverage and HIV prevalence, & characteristics associated with enrolment into HIV clinical care within two to four months after receiving an HIV diagnosis during HB-HTS among adult residents of a longitudinal Health and Demographic Surveillance System	15933	12035 (76%)	9895 (82%)	Adults & children[4] (≥13y)	NR	NR	NR	NR
Naik, 2015	To determine what proportion of adults LTC after HB-HTS within 3mths & the factors associated with LTC	NR	NR	NR	Adults (≥14y)	NR	NR	341 (224-542)	2

Tumwebaze, 2012	To evaluate HB-HTS combined with an electronic triage platform as a platform to facilitate LTC	1941	1587 (82%)	1558 (98%)	Adults (≥18y)	47% (n=724/1558)	479 (330–715)	NR	1
van Rooyen, 2014	To assess whether HB-HTS with POC CD4 & facilitated referrals to HIV care achieved: high HTS coverage; identified HIV-positive individuals unaware of their HIV status; reduced potential barriers to care engagement. & reduced infectiousness through high uptake of & adherence to ART	739	726 (98%)	671 (92%)	Adults (≥18yr)	33% (n=222/671)	435 (301–591)	NR	1
Shapiro, 2012 (non TB-contact households)	To determine the prevalence of undiagnosed TB & HIV in households of index TB-patients, to compare the yield of TB & HIV in TB-contact households with randomly selected non TB-contact households & determine the efficiency of targeting households of patients with TB for active case-finding interventions	NR	2843	1568 (55%)	Adults & children[4] (excl <5y)	NR	381 (236–567)	NR	1
Shapiro, 2012 (TB-contact households)			983	521 (53%)	Adults & children[4] (excl <5y)		383 (285–561)	NR	1
MacPherson, 2014	To investigate whether offering optional home initiation of ART after HIVST might increase population level ART uptake compared with HIVST combined with facility-based initiation	8466	Unknown (Test kits made available for 8466)	Unknown (Participant choice to disclose)	Adults (≥16y)	NR	NR	187 (100-256)	2
Community outreach and HB-HTS									
Barnabas, 2016	To assess whether community-based HTS with counsellor support and POC CD4 increases uptake of ART compared to HB-HTS	NR	15700	15332 (98%)	Adults (≥16y)	43% (n=6533/15332)	POC arm: 486 (344-653)	Clinic arm & could recall CD4: 512 (384-670)	1 & 2 (based on randomisation arm)
Parker, 2015 (HB-HTS)	To evaluate the feasibility, yield & LTC of two strategies: HB-HTS and community-based M-HTS	12269	7484 (61%)	7026 (94%)	Adults & children[4] (excl <5y)	39% (n=3106/7026)	NR	NR	2
Parker, 2015 (M-HTS)		18207	NR	2034	Adults & children[4] (excl <5y)	NR			2
Community outreach									
Bassett, 2014	To evaluate yield and LTC from M-HTS compared to clinic based HTS in high prevalence South African township	NR	NR	4703	Adults (≥15y)	46% (2163/4703)	416 (287-587)	NR	2

Chamie, 2012	To test the feasibility and diagnostic yield of integrating NCD and other communicable disease services into a rapid, high through-put, community based HIV testing and referral campaign for all residents of a rural Ugandan parish; and to determine rates and predictors of post-campaign LTC by disease	6300 (3150 adults)	4343 (2323 adults, 2020children)	2282 adults 1826children	Adults & children[4]	NR [5]	Adults: 415 (281-568)	NR	1
Govindasamy, 2013	To determine the yield of newly-diagnosed HIV, TB symptoms, diabetes & hypertension from a M-HTS unit, & assess CD4 testing, LTC & correlates of LTC & barriers to care	NR	9806	NR	Adults (≥18y)	NR	*Mean: 481 (95% CI: 458-505)*	NR	1
Hatcher, 2012	To assess predictors of LTC among individuals testing HIV-positive after community-based HTS	NR	NR	10203	Adults (≥18y)	NR	NR	NR	1
Kranzer, 2012	To compare yields of newly diagnosed HIV & advanced HIV between individuals attending M-HTS as participants in a population-based HIV seroprevalence survey & those accessing the service for routine HTS	NR	1300 (number recruited i.e. given flyer about M-HTS)	936 (included in LTC analysis)	Adults	Recruited HTS: 52% (n=491/936) Client-initiated HTS (not given flyer): 56% (n=488/877)	Recruited HTS: 385 (267–602) Client-initiated HTS: 415 (309-680)	NR	1
Labhardt, 2014 (M-HTS)	To compare HTS uptake, HIV prevalence and LTC within 1mth between HBHTS and M-HTS	4909	1392 (28%)	1207 (87%)	Adults & children[4]	Men (≥12yrs): 24% (n=236/994)	400 (207-629)	NR	1
Larson, 2012	To assess the proportion of patients LTC within 8wks of M-HTS under routine conditions & the impact of including POC CD4 testing on the proportion of patients LTC within 8wks of M-HTS	NR	NR	NR	Adults (≥18y)	NR	Among individuals offered POC CD4: 414 (251-589)	NR	1
van Zyl, 2015	To determine LTC & time to LTC after M-HTS combined with a call centre for facilitating LTC	NR	NR	NR	NR	NR	370 (IQR NR)	NR	NR

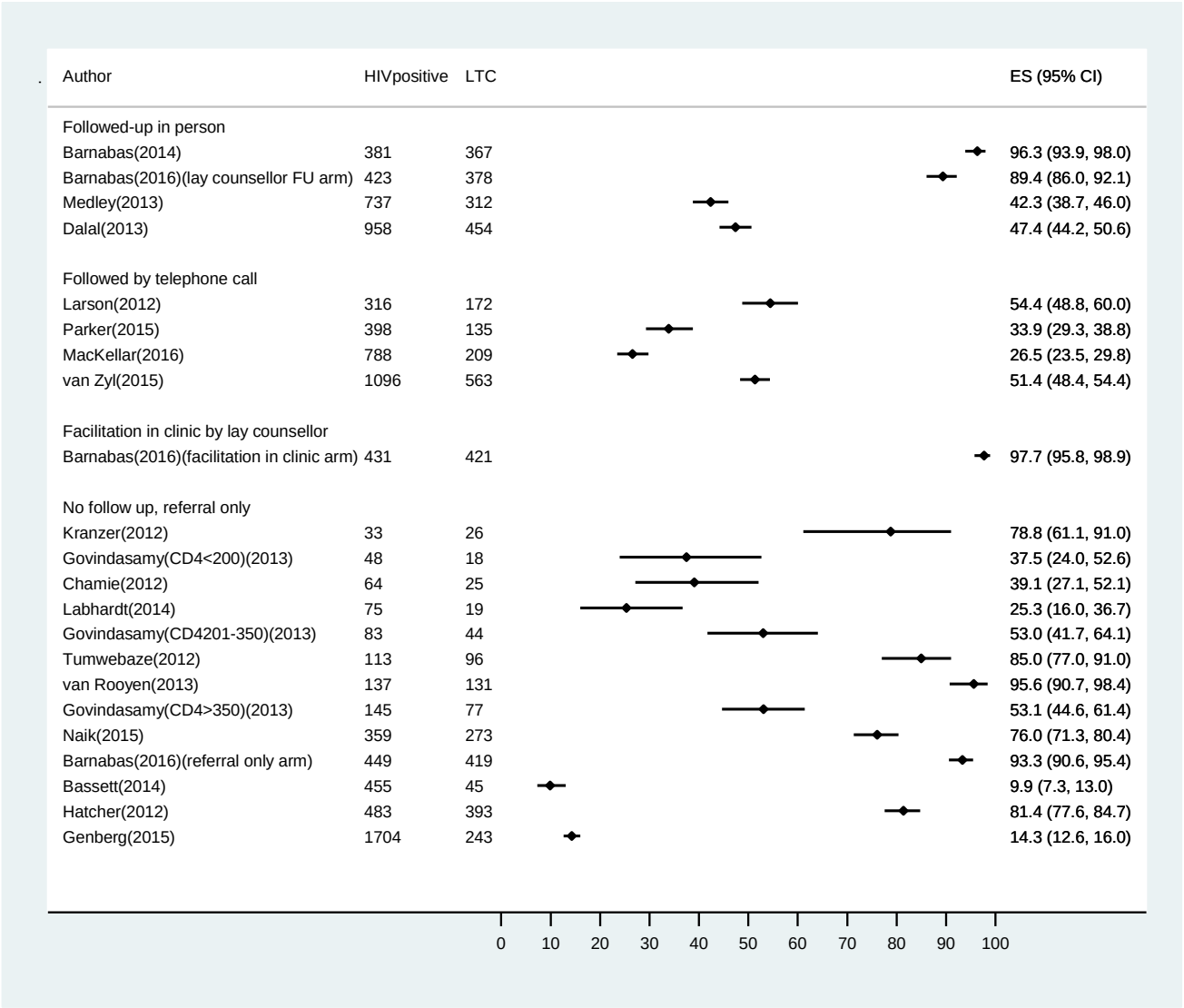
1. Percentage shown in brackets refers to proportion of population of offered testing among population served by HTS – if numerator and denominator reported in given study.
2. Proportion accepted testing among those offered HTS – if numerator and denominator reported.
3. Three studies also reported % of all men offered HTS who accepted testing: Dalal, 2013 - 80% (n=8889/11068); Labhardt, 2014 (HB-HTS) - 94%; (n=247/262); Labhardt, 2014 (M-HTS) - 97%; (n=236/243)
4. Children whose biological mother was deceased or known to be HIV+
5. Authors did not report% of males accepted but reported % of male residents who attended (were offered HTS) = 52% men (vs 95% of women)

Supplementary Figure 5.1: Flow diagram of study selection process

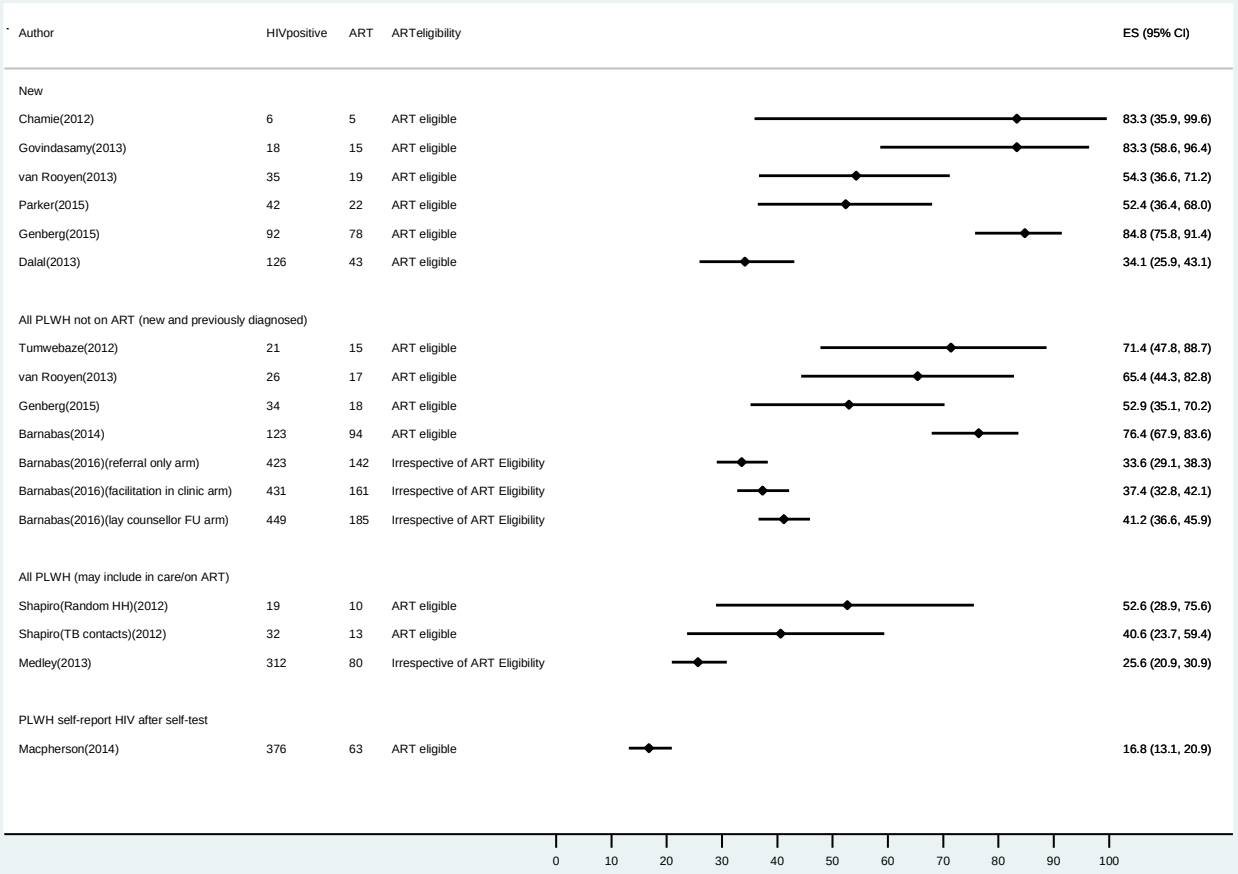


Supplementary Figure 5.2: Forest plots showing (a) LTC by method of follow-up (if any); (b) ART initiation outcomes by PLWH sub-groups; (c) ART initiation outcomes by when CD4-count result was available

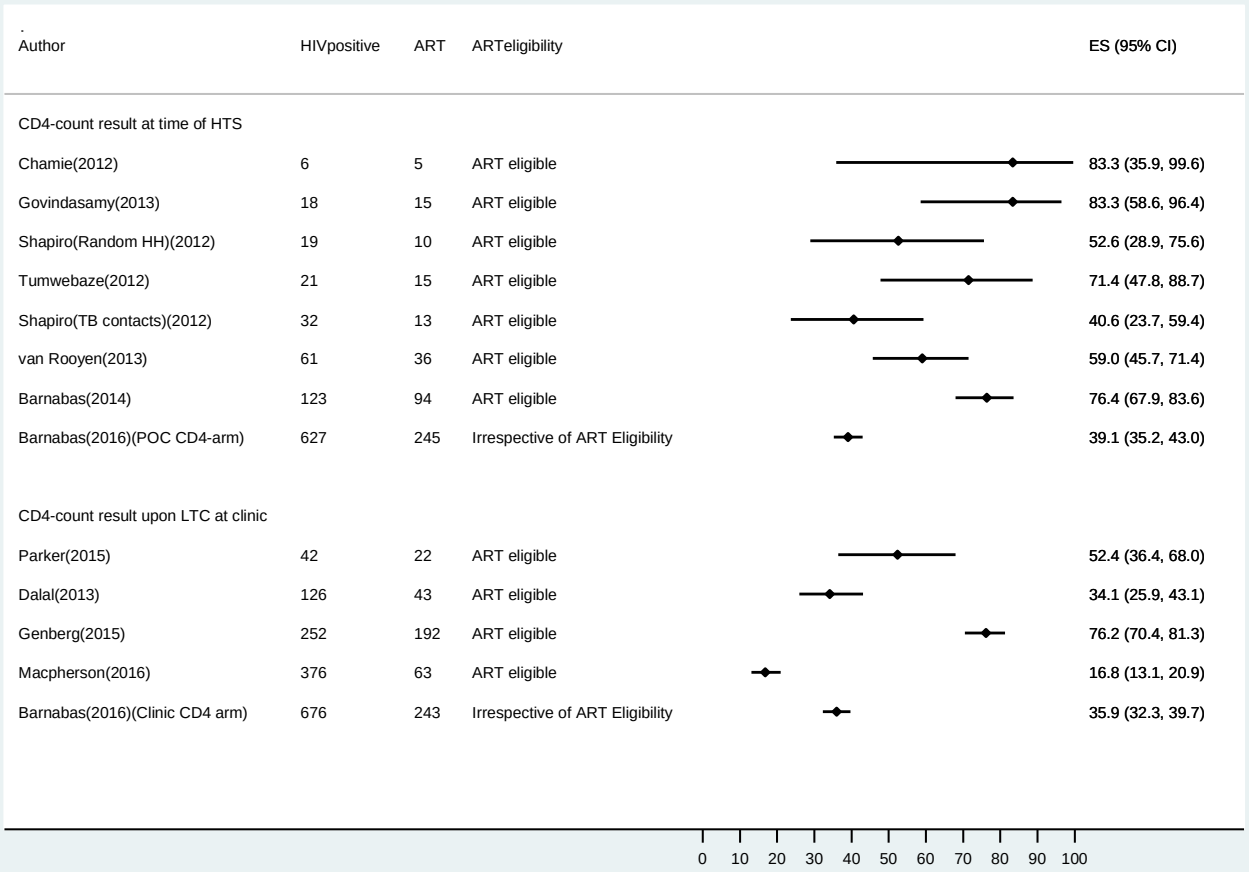
(a) Proportions LTC by method of follow-up



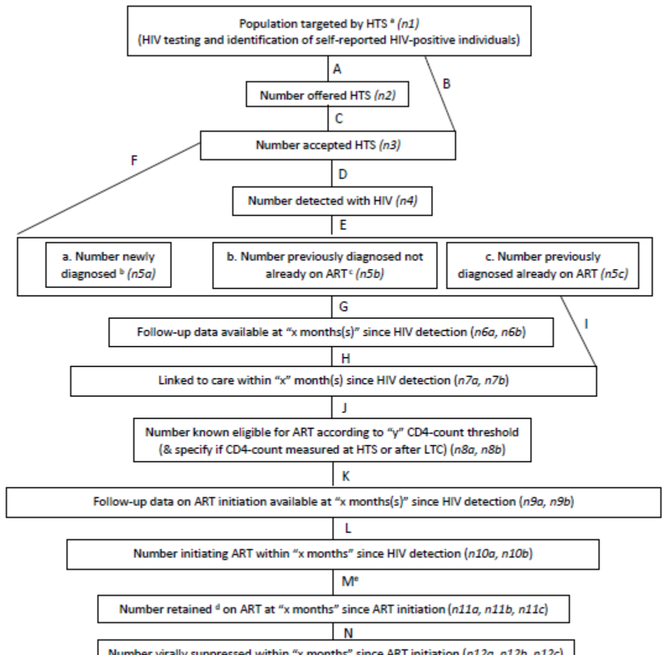
(b) Proportions initiating ART by PLWH sub-groups



(c) Proportions initiating ART by when CD4-count result was available



Supplementary Figure 5.3: Proposed standard indicators for future reporting



A. Proportion of target population offered HTS (*n2/n1*)
B. Population coverage of HTS (*n3/n1*)
C. Proportion accepted HTS among offered (*n3/n2*)
D. HIV-positivity in population accepting HTS (*n4/n3*)
E. Proportion of each HIV+ve sub-group (a.newly diagnosed; b. previously diagnosed not on ART; c.previously diagnosed already on ART) among those detected by HTS (*n5a/n4; n5b/n4; n5c/n4*)
F. Proportion of HIV+ve sub-group among those who accepted HTS (*n5a/n3; n5b/n3; n5c/n3*)
G. Proportion with follow-up data among respective sub-groups, at one or more of 1m / 3m / 6m / 12m (from when individual received HTS) [e] (*n6a/n5a; n6b/n5b; n6c/n5c*)
H. Proportion linked to care among those with follow-up data by respective sub-groups, at one or more of 1m / 3m / 6m / 12m (*n7a/n6a; n7b/n6b*)
I. Proportion linked to care among those detected with HIV by respective sub-groups, at one or more of 1m / 3m / 6m / 12m (*n7a/n5a & n7b/n5b*)
J. Proportion identified as eligible for ART initiation (100% if universal treatment applies) among those LTC by respective sub-groups, at one or more of 1m / 3m / 6m /12m (*n8a/n7a & n8b/n7b*)
K. Proportion on whom there is follow-up data on ART initiation, among those eligible (100% if universal treatment applies) by respective sub-group (*n9a/n8a & n9b/n8b*)
L. Proportion initiating ART among those eligible with follow-up data, by sub-group (*n10a/n9a & n10b/n9b*)
M. Proportion documented as retained on ART, by sub-group (*n11a/n10a, n11b/n10b, n11c/n5c*[e])
N. Proportion virally suppressed among those retained on ART, by sub-group (*n12a/n11a, n12b/n11b, n12c/n11c*)

a. Estimated or measured eg by census of target community b. Not self-reporting as HIV-positive c. This group could be further sub-divided into already in care (& not on ART) vs not already in care (& not on ART)
d. Retained = data confirming "on ART" in last 3 months e. For those previously started on ART – denominator is n5c and time since ART was first initiated

Supporting Information 5.1: Search terms and PRISMA checklist

Search Terms

Search terms for "The cascade-of-care following community-based detection of HIV – a systematic review with 90-90-90 targets in sight"

1. HIV

HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]

2. Home based

Home-based or home based or homebased OR door to door OR door-to-door OR home care services OR homecare services OR homecare OR home care OR home-care OR home access OR home OR in-home OR domicile

3. Community

Community* OR community based OR community-based OR mobile*

4. Work place

Work place OR work-place OR workplace OR work OR occupation*

5. School- based

School-based OR school OR school*

6. VCT

Voluntary Counselling or voluntary Counselling or voluntary Testing or hiv testing or Vct or hbvct or hct

7. Africa

sub-Saharan Africa OR south Africa OR Africa South of the Sahara OR Lesotho OR Swaziland OR Namibia OR Botswana OR Zimbabwe OR Mozambique OR Malawi OR Zambia OR Angola OR Tanzania OR Rwanda OR Burundi OR Democratic republic of Congo OR Republic of Congo OR Uganda OR Kenya OR Ethiopia OR Somalia OR Sudan OR Central African republic OR Cameroon OR Gabon OR Guinea OR Chad OR Nigeria OR Niger OR Togo OR Benin OR Ghana OR Burkina Faso OR Cote d'ivoire OR Ivory coast OR Liberia OR sierra Leone OR Senegal OR Gambia

8. (1 AND 5) AND (2 OR 3 OR 4 OR 5)
9. 8 AND 7
10. Limit 7 to 01/01/2006 to 01/03/2016

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P3 & 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P3 & 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P3 & 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Search Terms Suppl Mat
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P3 & 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P3 & 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P3 & 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P3 & 4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P4 & Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P4 & Suppl Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P4-8 & Table 1 & 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P4-8, Table 1 & 2, Fig 1 &2, Suppl Fig 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P8-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P8-10 Suppl Fig 3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P11-12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Chapter 6: Predictors of timely linkage-to-ART within universal test and treat in the HPTN 071 (PopART) trial – findings from a nested case-control study

Outline of chapter

The second of two case-control studies for this PhD was done to examine the factors associated with timely linkage to care and ART initiation during the first annual round of PopART. Presented below is the manuscript on the study which has been submitted to the Journal of International AIDS Society.

6.1 Abstract

Introduction

This study examined factors associated with timely linkage-to-care and ART initiation (TLA) (i.e. within 6-months of referral) in the context of universal test and treat (UTT) within the intervention communities of the HPTN 071 (PopART) trial.

Methods

Of 7,572 individuals identified as PLWH (not on ART) during the first year of the PopART intervention provided by Community HIV-care Providers (CHiPs) through door-to-door household visits, individuals who achieved TLA (controls) and those who did not (cases), stratified by gender and community, were randomly selected to be re-contacted for interview. Standardised questionnaires were administered to explore factors potentially associated with TLA, including demographic and behavioural characteristics, and participants' opinions on HIV and related services. Odds ratios comparing cases and controls were estimated using multi-variable logistic regression.

Results

Data from 705 participants (333 cases/372 controls) were analysed. There were negligible differences between cases and controls by demographic characteristics including age, marital or socio-economic position. Prior familiarity with the CHiPs encouraged TLA (AOR of being a case: 0.58, 95%CI: 0.39-0.86, p=0.006).

Participants who found clinics overcrowded (AOR: 1.51, 95%CI: 1.08-2.12, p=0.006) or opening hours inconvenient (AOR: 1.63, 95%CI: 1.06-2.51, p=0.02) were less likely to achieve TLA, as were those expressing stronger feelings of shame about having HIV (ptrend=0.007). Expressing "not feeling ready" (AOR: 2.75, 95% CI: 1.89-4.01, p<0.001) and preferring to wait until they felt sick (AOR: 2.00, 95% CI: 1.27-3.14, p=0.02) were similarly indicative of being a case. Worrying about being seen in the clinic or about how staff treated patients were not associated with TLA.

While the association was not strong, we found that the greater the number of self-reported lifetime sexual partners the more likely participants were to achieve TLA (ptrend=0.06). There was some evidence that participants with HIV-positive partners on ART were less likely to be cases (AOR: 0.75, 95% CI: 0.53-1.06, p=0.07)

Discussion

The lack of socio-demographic differences between cases and controls is encouraging for a "universal" intervention that seeks to ensure high coverage across whole communities. Making clinics more "patient-friendly" could enhance treatment uptake further. The finding that those with higher risk behaviour are more actively engaging with UTT holds promise for treatment-as-prevention.

6.2 Introduction

The concept of universal test and treat (UTT) has been widely promoted for approximately the last decade and definitive evidence for the efficacy of treatment as prevention at the level of individual partnerships has been available since the results of the HPTN (HIV Prevention Trials Network) 052 trial were announced in 2011.(1, 2) Other studies have since provided clear evidence on the benefit of early treatment for the health of the person living with HIV (PLWH).(3, 4) The World Health Organization (WHO) has revised its guidelines, to recommend that all PLWH be offered antiretroviral treatment (ART) irrespective of CD4 count, also known as "immediate treatment".(5)

The HPTN 071 (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART)) trial has been underway in 21 communities in Zambia and South Africa to examine the impact of a combination prevention package including UTT on HIV-incidence at a community level. The trial consists of three arms as described elsewhere (6) and illustrated in Figure-1, and the full intervention arm (Arm A) has offered UTT from the launch of the trial in 2014.

In order for UTT to have maximal impact in reducing community-level HIV-incidence, uptake of treatment would have to be wide-spread across subsets of the population with different socio-demographic and behavioural characteristics. There is evidence on factors associated with initiation of ART, usually among individuals who have already linked-to-care at least once since HIV diagnosis and from contexts where ART eligibility criteria applied. (7-12) More scarce are data from settings providing immediate treatment or UTT, with the latter not only making ART immediately available for all who have already presented to health-facilities, but first seeking to test everyone in the community (universal testing). (13) Although a UTT approach substantially simplifies treatment by removing ART initiation criteria, providers must still negotiate all the steps along the cascade of care, to link clients to care following HIV detection in the community and achieve timely initiation of ART. It also involves attempting to initiate treatment in a timely fashion, in individuals who were diagnosed as part of a universal testing programme in the community, who may not otherwise have sought to find out their HIV status. While this helps achieve universal knowledge of HIV status and identify as many PLWH as possible, it may also pose challenges for treatment readiness – in addition to other potential barriers.

The study described here examined the factors associated with the uptake of universal treatment, specifically timely linkage-to-care and initiation of treatment (which we will refer to as timely linkage-to-ART (TLA)) following door-to-door universal testing, during the first year of the PopART UTT intervention.

6.3 Methods

The nested case-control study was carried out in PopART Arm A communities which offered UTT - four in Zambia and three in South Africa (Figure-1). The study objectives were to identify differences between those who had not achieved TLA (cases) and those who had done so (controls). TLA was defined as linkage-to-care and initiation of ART within 6 months of referral by Community HIV-care Providers (CHiPs).

CHiPs (lay counsellors employed and trained to work in their own communities), provided a door-to-door community-based package of services (Figure-1) and captured the details of all individuals who consented to the PopART intervention on an electronic register.(6) During the initial CHiP home visit, HIV was detected through HIV testing and counselling (HTC) or by individuals self-reporting HIV-positive status. All PLWH who were not on ART were offered referral to the local health-facility for linkage-to-ART. Follow-up home visits were conducted to ascertain linkage and ART initiation outcomes and recorded in the CHiP electronic register.

Community members who were referred between January 2014-January 2015, during the first year of the PopART intervention and had had at least 6 months to achieve TLA (by July 2015) were eligible for the case-control study. Further, participants had to be ≥18 years old and be able and willing to provide informed consent.

The data on TLA entered at a follow-up home visit by CHiPs, more than 6 months after referral (to allow time for TLA), were used as a starting point for random selection of study participants. Participants who had achieved TLA within 6 months of referral by CHiPs were eligible to be controls; individuals who had been followed up after 6 months but had not started ART at all or only started after 6 months were potential cases. Random samples of those who did not manage TLA (cases) were selected, stratified by community and gender, to have adequate representation of individuals from all the PopART intervention communities and from both genders. An equal number of gender-matched individuals per community, who did manage TLA (controls) were then randomly selected.

A sample in excess of the number required for recruitment was selected in anticipation of difficulties in finding participants – given the mobility and migration in the study communities. Due to a wide range in community sizes, the numbers of individuals meeting the case and control definition varied across communities and some communities had fewer individuals than required by the study while others had much larger numbers. This meant that in the smaller communities everyone who had been referred was selected, rather than a random subset.

Verbal permission to allow case-control (CC) field research assistants (RAs) to approach participants was obtained by the CHiP staff who had previously referred individual community members for TLA. Written informed consent for study participation was then obtained by CC study RAs. RAs conducted electronically administered surveys with standardised questionnaires. Questionnaire themes were informed by current evidence in the literature and anecdotal local information on factors that may influence TLA. Participants' case or control status was not given to RAs.

The final sample size of ~700 participants (1:1 case: control ratio) provided just over 80% study power to detect associations with odds ratios of ~1.75 or higher (or ~0.5 or lower), for explanatory variables with 15% prevalence in controls ($\alpha = 0.05$). Odds ratios were estimated using multivariable logistic regression and all models included community and gender to account for the frequency-matched sampling strategy. Age category was then included as an a priori potentially confounding variable. Additional variables which showed at least weak evidence of association with TLA were included as appropriate. Likelihood ratio testing (LRT) was done to assess the statistical evidence of association. Evidence of interaction with gender and country was explored. For variables with three or more response categories and potential for a dose-response relationship, tests for trend were performed.

The study was approved by the ethics committees of the University of Zambia, Stellenbosch University and London School of Hygiene and Tropical Medicine.

6.4 Results

Demographic, sexual behaviour and health-related characteristics

During the first year of the PopART intervention 152,383 individuals consented to participate in the PopART intervention in the 7 arm A communities. Of these, 16,112 individuals (5,028 men and 11,084 women) were identified as living with HIV (newly diagnosed or self-report of known HIV-positive status) and 7,572 were referred to HIV care, among those not on ART at the time of referral. After allowing at least 6 months for TLA, 5,161 were documented as either having started ART within 6 months after referral, or were followed up >6 months after referral and had not started ART. Of these, 2,444 individuals (781 men and 1,663 women) had linked-to-care and initiated ART within 6 months of referral and 2,717 had not.

Of the 2,717 potential cases who did not achieve TLA, 908 were randomly selected to be contacted by CHiPs, and 437 (48%) were found and agreed to be contacted by the CC field research assistants (RAs). Of them, 333 (76%) cases consented to participate in the study (Figure-2a). Of 812 potential

controls who achieved TLA and were randomly selected, 460 (57%) agreed to be contacted by the CC RAs and a slightly greater proportion were successfully recruited (372 (81%)) (Figure-2b).

Data from 705 participants were included in the final analysis – 79% (555) from four communities in Zambia and 21% (150) from three communities in South Africa. There were fewer men (~40%) than women (~60%) in the study, but proportions were balanced by case/control status (Table-1). When compared with the randomly selected sample, there was a lower proportion of 18-24 year olds in the final study population (10% vs 18% of both cases and controls) and a higher proportion of ≥45 year olds (22% vs 11% among cases, and 25% vs 15% among controls).

Most participants were married, had had primary education only and were unemployed (2% of all participants were students). There were no differences by case/control status for any of these demographic characteristics, overall.

The majority of participants reported 2-5 lifetime sexual partners and the number of partners was associated with case/control status. There is a suggestion of a trend that the greater the number of partners the more likely participants were to achieve TLA (with diminishing odds ratios (AORs) of being a case, ptrend=0.06) (Table-1).

The HIV and ART status of the participant's main partner (of the last 12 months) was associated with case/control status. Compared to those who did not report having a known HIV-positive partner, participants who had HIV-positive partners not on ART (although there were relatively few in that category) were twice as likely to be cases themselves (AOR:2.02,95% CI:1.11-3.66,p=0.02). Participants whose HIV-positive partners were on ART were less likely to be cases (OR: 0.70, 95% CI: 0.50-0.98, p=0.04), but the evidence of association was weaker in the adjusted model (AOR: 0.75, 95% CI: 0.53-1.06, p=0.07).

Participants who had previously linked-to-care (prior to CHiP referral) and were still in care (but not on ART) when the initial CHiP home visit was conducted were less likely to be cases than those who had never previously linked, as might be expected (AOR: 0.60, 95% CI: 0.38-0.96, p=0.03). Although there were relatively few participants who reported that they had previously linked but had defaulted from care, when compared against those who had never linked there was no evidence of a difference (AOR: 0.79, 95% CI: 0.42-1.47, p=0.45) (Table-1). There was no relationship between latest CD4-count (self-reported at the time of the CC study by those who had had it done) and case/control status. However, not having had a CD4-count done or not knowing one's result was predictive of being a case (AOR: 1.94, 95% CI: 1.18-3.21, p=0.009) when compared with those who had a CD4-count which was low (0-350/cc3).

Participants' perceptions of HIV service factors which may affect TLA

Cases and controls were asked (identical) standardized questions about factors that encourage TLA (regardless of whether TLA was achieved). Prior familiarity with the CHiP who delivered the intervention encouraged TLA (AOR of being a case: 0.58, 95% CI: 0.39-0.86, p=0.006) (Table-2). The majority of participants accepted HIV testing with the CHiP, and this appears to be associated with being a case, although not reaching statistical significance in the adjusted model (AOR:1.60,95% CI:0.95-2.70,p=0.07) when compared with individuals who self-reported HIV-positive status .

Participants who reported time constraints due to work or housework as a factor which discouraged linkage-to-care were more likely to be cases (AOR:1.64,95% CI:1.14-2.38,p=0.02). When restricted to those who had not previously linked-to-care prior to the CHiP referral (N=603), a number of factors related to accessing the clinic, including inconvenient clinic opening hours (AOR:1.63,95% CI:1.06-2.51,p=0.02); overcrowding in the clinic (AOR:1.51,95% CI:1.08-2.12,p=0.006); and distance/ time to travel to clinic (AOR:2.55,95% CI:1.14-5.69,p=0.009) were associated with being a case (although very few complained of the latter in the urban and peri-urban settings that characterize all our communities) (Table-2). Expressing "not feeling ready" (AOR: 2.75, 95% CI: 1.89-4.01, p<0.001) and preferring to wait until they felt sick (AOR: 2.00, 95% CI: 1.27-3.14, p=0.02) were similarly indicative of being a case. Neither being worried about being seen in the clinic or perceptions about how staff treated patients were associated with TLA (data not shown).

Perceived advantages and disadvantages to the individual of achieving TLA (including stigmatizing attitudes)

Participants who said that they would start ART for their own health, even without feeling unwell, were more likely to achieve TLA (AOR of being a case:0.53,95% CI:0.38-0.75,p<0.001) as were those who said they would comply with CHiPs/clinic staff's advice to link-to-ART without delay (AOR of being a case:0.56,95% CI:0.34-0.91,p=0.02). There was weak evidence that knowing others who were well on ART (AOR: 0.74, 95% CI: 0.53-1.03, p=0.08) encouraged TLA. There was no strong association between case/control status and stating that protecting a partner from acquiring HIV was a factor which encouraged TLA (AOR: 0.81, 95% CI: 0.58-1.12, p=0.19) (Table-3).

As was seen with "not feeling ready" to link to care (Table-2), "not feeling ready" to take ART was also associated with being a case (AOR: 2.25, 95% CI: 1.58-3.21, p<0.001). The idea of taking life-long treatment also appeared to be a deterrent to TLA (AOR: 1.44, 95% CI: 1.00-2.07, p=0.05) (Table-3).

Stigmatising attitudes were not generally seen to affect TLA (Table-3 and other data not shown). However, the more strongly participants agreed with a statement about feeling ashamed because they were HIV-positive, the more likely they were to be a case (test for trend p=0.007).

Differences in association by gender and country

There was no statistical evidence of differences in association by country but shown in Supplementary Table-1 are associations which were seen to differ by gender. While there was no association between education of participants overall and of women alone with case/control status, men who had secondary education appeared more likely to be cases than men with primary education (AOR: 2.50, 95% CI: 1.30-4.82, p=0.02). However, there was no clear trend seen across educational strata and it is possible that this association was a chance finding. Amongst men but not amongst women, being familiar with the CHiP prior to the initial PopART home visit was strongly associated with TLA (AOR of being a case among men: 0.29, 95% CI: 0.14-0.58, p<0.001).

The majority of participants irrespective of gender or case/control status had disclosed their HIV status to someone. Amongst women, there was statistical evidence of disclosure encouraging TLA (AOR of being a case: 0.18, 95% CI: 0.09-0.36, p<0.001) while the association was weak among men. Men who had a high AUDIT (Alcohol Use Disorders Identification Test) score (≥ 8) which denoted hazardous and harmful alcohol use (14), and possible dependence, were more likely to be cases (AOR: 2.13, 95% CI: 1.20-3.81, p=0.009) than men with lower scores (≤ 7), while this was not the case among women who drank excessively.

6.3 Discussion

This study examined factors associated with the timely initiation of ART in high HIV prevalence settings in sub-Saharan Africa, in greater detail than any other published study we are aware of. It provides novel insights into TLA in the context of UTT, with participants identified with HIV during universal door-to-door home-based HIV testing. We have examined the combined outcome of TLA which requires linkage-to-care following HIV detection and referral in the community, and initiation of ART in the health facility, all within a relatively short period (6 months). The predictors of TLA we have examined may have influenced either linkage to care or ART initiation or both. Only one other study we are aware of has examined factors associated with “linkage-to-ART”. (15) Other studies have focused instead either on predictors of linkage-to-care or on predictors of initiation of ART among those already linked-to-care or diagnosed in health facilities. Yet, as community-based HIV testing becomes widespread in high HIV prevalence settings, combined with immediate eligibility for ART, we consider that it is pertinent to examine TLA - to effect meaningful change in ART coverage with a view to achieving the “second 90” of the UNAIDS 90-90-90 targets. (16)

Our study found no evidence of associations between demographic or socio-economic characteristics and TLA, similar to reported findings from other settings. (7, 10, 11, 13) This is encouraging for a "universal" intervention that seeks to ensure high coverage across the whole of the community. Having favourable views about the PopART CHiPs appears to facilitate TLA - with prior familiarity with the CHiPs (as fellow community members), feeling comfortable talking to the CHiPs and accepting their advice, all encouraging TLA. Few participants complained of healthcare worker factors as barriers to linking-to-care. Clinic infrastructure factors however were cited as disincentives (inconvenient clinic opening hours, over-crowding, etc.).

While the evidence of associations was not strong we found that behavioural factors, including self-reported sexual behaviour and HIV related behaviour (namely disclosure of HIV status) influenced TLA. Those reporting a greater number of lifetime sexual partners were more likely to succeed with TLA. This suggests that the self-acknowledged perception that one might be at risk of HIV, facilitated linkage and ART initiation. One possible explanation is that these individuals were more willing to acknowledge living with HIV and hence achieved TLA more readily. Consistent with this explanation is the finding that those who reported "not feeling ready" or who said they would only start treatment once they felt sick, were less likely to achieve TLA. The finding that those with higher risk behaviour are more actively engaging with UTT is encouraging for treatment as prevention.

Corroborating the findings of the study by Boyer et al. on ART initiation (among those linked-to-care) in another UTT trial, we found that disclosure of HIV-status facilitated TLA. (13) Along a similar theme, participants who reported that they had an HIV-positive partner on ART were more likely to succeed with TLA themselves, while the opposite was true if they had an HIV-positive partner who was not ART. Our data also indicate that participants who reported that they had disclosed their HIV-positive status were more likely to report a partner on ART than those who had not disclosed (36% vs 17%, respectively $p<0.001$). Protecting a partner from acquiring HIV as a reason to start ART was not associated with increased TLA (Table 3), and this may suggest that greater efforts to promote a "treatment for prevention" message are indicated.

The high proportion of men overall who had high AUDIT scores is alarming (51%), although the prevalence in women (20%) is also substantial. The difference in association of alcohol excess with TLA by gender is interesting. Men with high AUDIT scores were more likely to be cases, and this suggests that provision of integrated alcohol reduction/treatment and HIV prevention/treatment programmes that target men should be explored. Among women, the evidence was of a weak association in the opposite direction. A possible explanation is that men with heavy alcohol consumption avoided engagement with treatment and care, while women who drank heavily may

have sought health-care/treatment as a way to compensate for “unhealthy” behaviour. Further, among women (but not men) a higher proportion of those who were heavy drinkers considered themselves at high risk of acquiring HIV infection compared to those who were non-heavy drinkers (59% vs 42%, p=0.005). This association among women is consistent with our finding above that high risk perception may encourage treatment engagement.

Our data indicate that stigma overall is not a major barrier to TLA, but internalized stigma (i.e. taking on and believing to be true, the negative beliefs and attitudes about PLWH) may have an influence. This is said to be one of the most insidious aspects of stigma, as it somehow makes PLWH feel “less human”.(17) There is evidence to suggest that support groups can help mitigate this form of stigma.(18, 19)

Our study had several limitations. Only participants who agreed for the study research team to contact them could be recruited into the study. This means that individuals who could not be contacted, or declined or avoided contact would not be represented in the study, nor would those who declined to consent once contacted. While this is common to many community-based survey studies, the representativeness of the study sample must be borne in mind as a limitation of the study. We did see evidence of differential selection of potential participants by case/control status with a higher proportion of randomly selected potential controls recruited than randomly selected potential cases (46% vs 37%). As described earlier there were also fewer men than women in the study sample despite frequency matching on gender when randomly selecting the sample. Young people were also somewhat under-represented in the final study sample. Both of these are likely due to the fact that the study was conducted in the household and men and younger people are less likely to be found at home than older people. Reporting bias and social desirability bias are both possibilities, in common with most research using self-reported data. However, given the wide range of themes explored by the questionnaire and the lack of an obvious single hypothesis, these biases are unlikely to be differential based on case or control status of the participant. Reverse causality must also be borne in mind given that the CC study was conducted a period of time after the referral for HIV care. Further, given the case-control design causality cannot be inferred from our findings and we are limited to observing associations.

The strengths of this study have already been alluded to – including the breadth and depth of the themes explored, the novelty of examining TLA under UTT conditions and the focus on TLA as a combination of both timely linkage-to-care and ART initiation, given that community-based testing is becoming increasingly prevalent. In addition, we had a sizeable proportion of men (~40%) who are often under-represented. Our study was conducted in large urban and peri-urban communities and

this provides a good basis for generalizability for the majority of those living with HIV in sub-Saharan Africa.

Further research is required to explain some of the results. For instance, even though familiarity with the CHiPs encouraged TLA, there is a suggestion in our data that having an HIV test with the CHiP was associated with being a case i.e. failure to achieve TLA. This is most likely due to the fact that those who tested with CHiPs were the ones receiving new diagnoses of HIV infection, and needing time to become comfortable with the idea of needing treatment, whereas those who did not test with CHiPs were the ones who already knew their HIV positive status and may have been more ready for TLA. However, this warrants further enquiry.

In summary, our study findings suggest that the universal treatment intervention within PopART did not systematically exclude any subsets of the population and it has the potential to be universally acceptable. The finding that those who reported having an HIV-positive partner not on ART were less likely to achieve TLA points to the cumulative gains to be won by initiating individuals on ART – as it may have the added benefit that their partner would be encouraged to do so as well. As holding a favourable view of the CHiPs was associated with successful TLA, we recommend investment in the cadre of staff delivering services as a means to increase uptake. The concerns expressed by participants about health-facilities warrants both on-going improvement of infrastructure and innovative means to reduce the burden on clinics by providing care in the community for patients who are stable and comfortable with non-clinic based care.

The findings that higher risk sexual behaviour may be associated with more timely linkage-to-ART holds great promise for the effectiveness of UTT in achieving reductions in HIV-incidence at the community level. Overall, we found few fundamental differences between those who linked-to-ART in a timely fashion and those who did not, but the differences we did uncover provide opportunities to achieve universal treatment coverage within the framework of universal test and treat.

Conflicts of interests

We have no conflicts of interests to declare.

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Authors' contributions:

KS with oversight from RH, designed the study, led on writing and revising the paper and led on the statistical analysis of the data. CMM, CM and GH were involved with leading field data collection and ensuring the quality of data. AS(1) led on programming of study tools and had over-sight of the random selection of participants and data management. AS(2) provided expert advice to the stigma related content of the study. SF(1) provided specific advice on statistical methods and along with SF(2) and HA, guidance on study themes and implementation. All authors contributed to the writing of the paper and have read and approved the final manuscript.

6.6 References:

1. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England journal of medicine. 2011;365(6):493-505.

2. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657):48-57.

3. INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The New England journal of medicine. 2015;373(9):795-807.

4. TEMPRANO ANRS Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. The New England journal of medicine. 2015;373(9):808-22.

5. World Health Organization. Guideline on when to start Antiretroviral therapy and on Pre-exposure Prophylaxis for HIV. http://appswhoint/iris/bitstream/10665/186275/1/9789241509565_engpdf?ua=1. 2015;Accessed on 26th February 2016.

6. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial. Trials. 2014;15:57.

7. Aliyu MH, Blevins M, Parrish DD, Megazzini KM, Gebi UI, Muhammad MY, et al. Risk factors for delayed initiation of combination antiretroviral therapy in rural north central Nigeria. Journal of acquired immune deficiency syndromes. 2014;65(2):e41-9.

8. Amuron B, Namara G, Birungi J, Nabiryo C, Levin J, Grosskurth H, et al. Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda. BMC public health. 2009;9:290.

9. Feldacker C, Johnson D, Hosseinipour M, Phiri S, Tweya H. Who starts? Factors associated with starting antiretroviral therapy among eligible patients in two, public HIV clinics in Lilongwe, Malawi. PloS one. 2012;7(11):e50871.

10. Fox MP, Shearer K, Maskew M, Meyer-Rath G, Clouse K, Sanne I. Attrition through multiple stages of pre-treatment and ART HIV care in South Africa. PloS one. 2014;9(10):e110252.

11. Katz IT, Essien T, Marinda ET, Gray GE, Bangsberg DR, Martinson NA, et al. Antiretroviral therapy refusal among newly diagnosed HIV-infected adults. Aids. 2011;25(17):2177-81.

12. McGrath N, Glynn JR, Saul J, Kranzer K, Jahn A, Mwaungulu F, et al. What happens to ART-eligible patients who do not start ART? Dropout between screening and ART initiation: a cohort study in Karonga, Malawi. BMC public health. 2010;10:601.

13. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS care. 2016;28 Suppl 3:39-51.

14. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test - Guidelines for Use in Primary Care. http://appswhoint/iris/bitstream/10665/67205/1/WHO_MSD_MSB_016apdf. 2001;Accessed on 6th Feb 2017.

15. MacPherson P, MacPherson EE, Mwale D, Bertel Squire S, Makombe SD, Corbett EL, et al. Barriers and facilitators to linkage to ART in primary care: a qualitative study of patients and providers in Blantyre, Malawi. Journal of the International AIDS Society. 2012;15(2):18020.

16. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. http://wwwunaidsorg/sites/default/files/media_asset/90-90-90_en_0pdf. 2014;Accessed on 11th January 2016.

17. E. G. Stigma: Notes on the Management of Spoiled Identity. 1963.

18. Rao D, Desmond M, Andrasik M, Rasberry T, Lambert N, Cohn SE, et al. Feasibility, acceptability, and preliminary efficacy of the unity workshop: an internalized stigma reduction intervention for African American women living with HIV. AIDS patient care and STDs. 2012;26(10):614-20.

19. Stangl AL, Lloyd JK, Brady LM, Holland CE, Baral S. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? Journal of the International AIDS Society. 2013;16(3 Suppl 2):18734.

Figure 6.1: PopART trial schema

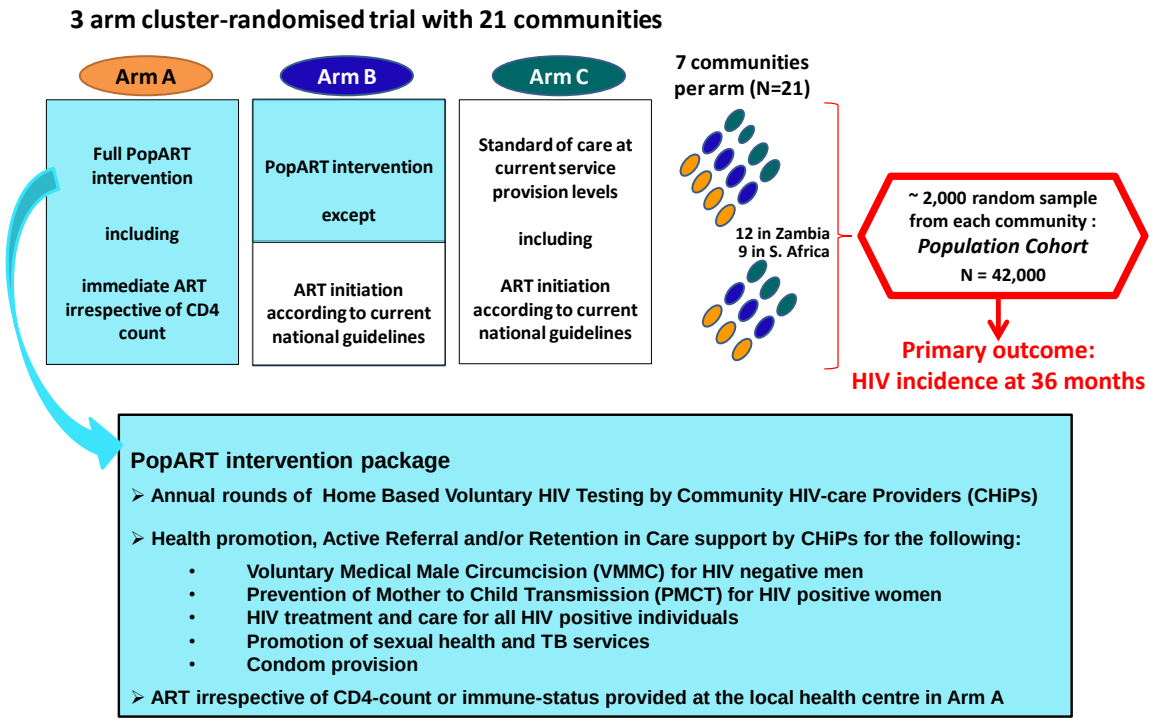
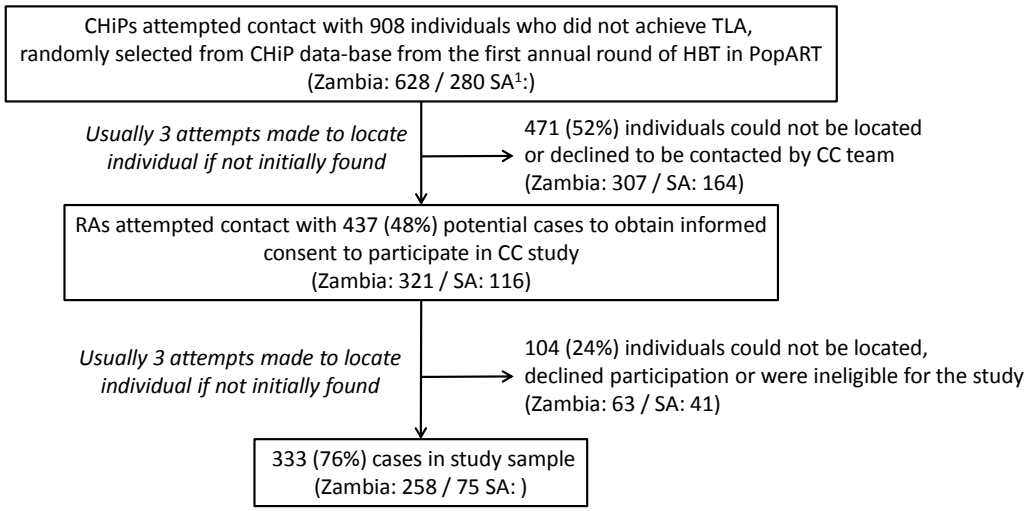
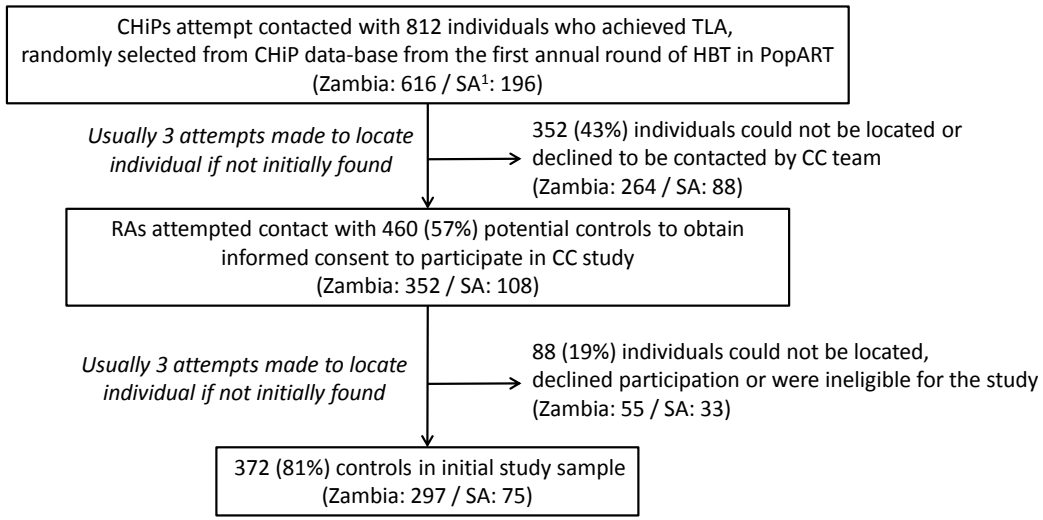


Figure 6.2a – Case (did not achieve TLA i.e. did not initiate ART or initiated more than 6m after CHiP referral) selection process and sampling fraction



1. SA = South Africa

Figure 6.2b – Control (achieved TLA i.e. initiated ART within 6m of CHiP referral) selection process and sampling fraction



1. SA = South Africa

Table 6.1: Demographic, sexual behaviour and health related characteristics of cases and controls

	Controls (Achieved TLA) N (%)	Cases (Did not achieve TLA) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio [3]	*LRT [2] p-value*, 95 % Confidence Interval
Total						
Gender [4]						
Male	151 (41)	132 (40)				
Female	220 (59)	201 (60)				
Demographic and socio-economic characteristics						
Age category						
18 – 24 years	36 (10)	32 (10)	1	*0.86*	1	*0. 60*
25 – 34 years	129 (35)	118 (35)	1.04	0.60-1.80	1.05	0.59-1.89
35 – 44 years	115 (31)	110 (33)	1.08	0.61-1.89	1.08	0.60-1.95
≥ 45 years	92 (25)	73 (22)	0.91	0.50-1.63	0.82	0.45-1.52
Marital status						
Never married	48 (13)	55 (16)	1	*0.48*	1	*0.27*
Currently married	215 (58)	184 (55)	0.75	0.46-1.21	0.77	0.45-1.32
Previously married [5]	109 (29)	94 (28)	0.75	0.44-1.28	0.63	0.35-1.12
Educational attainment						*P_{trend} [6] 0.11*
Primary (Grade 0-7)	183 (49)	153 (46)	1	*0.76*	1	*0.21*
Junior secondary (Grade 8-9)	94 (25)	84 (25)	1.09	0.75-1.58	1.15	0.77-1.72
Senior secondary (Grade 10-12) or higher education	94 (25)	96 (29)	1.22	0.83-1.78	1.45	0.96-2.19
Employment						
None	181 (49)	166 (50)	1	*0.42*	1	*0.41*
Casual/seasonal/occasional	61 (16)	60 (18)	1.12	0.71-1.75	1. 18	0.74-1.89
Self employed	67 (18)	64 (19)	1.12	0.73-1.73	1.22	0.77-1.92
Formal wage	63 (17)	43 (13)	0.75	0.47-1.19	0.79	0.49-1.29
SES (PCA[7] of HH factors & assets [8])						
Lower	181 (49)	176 (53)	1	*0.27*	1	*0.43*
Higher	191 (51)	157 (47)	0.84	0.61-1.15	0.87	0.63-1.22
Sexual behaviour						
No of lifetime sexual partners						*P_{trend} [6] 0.06*
1	33 (9)	47 (14)	**1**	***0.02***	**1**	***0.04***
2 - 5	221 (60)	192 (58)	**0.57**	**0.34-0.93**	**0.55**	**0.33-0.92**
6 - 9	49 (13)	48 (14)	0.59	0.30-1.13	0.56	0.28-1.10
≥ 10	68 (18)	45 (14)	**0. 40**	**0.21-0.75**	**0.38**	**0.19-0.74**
Self-assessment of sexual risk ("My sexual behaviour (incl. partner(s) I have had), has put me at risk of getting HIV")						
Low	180 (49)	181 (55)	1	*0.08*	1	*0.13*
High	191 (51)	151 (45)	0.75	0.55-1.03	0.77	0.55-1.08
HIV and health factors						
Has HIV status been disclosed to anyone						
N	38 (10)	74 (22)	**1**	***<0.001***	**1**	***<0.001***
Y	334 (90)	259 (78)	**0.39**	**0.25-0.59**	**0.39**	**0.25-0.60**
HIV & ART status of spouse/main partner [9] (in last 12m)						
No sexual partner in last 12m / partner HIV status not known or reported HIV negative	214 (58)	204 (61)	1	***0.002***	1	***0.005***
HIV positive partner - not on ART	20 (5)	37 (11)	**1.96**	**1.10-3.49**	**2.02**	**1.11-3.66**
HIV positive partner - on ART	138 (37)	92 (28)	**0. 70**	**0.50-0.98**	0.72	0.51-1.03
Had participant linked to care prior to referral by CHiP						
Not linked prior to CHiP	280 (75)	274 (82)	1	***0.04***	1	*0.09*
Linked prior to CHiP but not in care when referred	29 (8)	21 (6)	0. 70	0.38-1.28	0.79	0.42-1.47
Linked prior to CHiP and in care when referred (not self-reported on ART)	63 (17)	38 (11)	**0.59**	**0.38-0.92**	**0.60**	**0.38-0.96**
Most recent CD4-count						
0-350	60 (16)	34 (10)	**1**	***<0.001***	**1**	***<0.001***
351-500	44 (12)	18 (5)	0.72	0.36-1.46	0.69	0.33-1.43
≥501	53 (14)	34 (10)	1.17	0.63-2.16	1.17	0.62-2.20

Not done / don't know CD4-count	215 (58)	247 (74)	**2.21**	**1.37-3.58**	**1.94**	**1.18-3.21**
Health in last 12m						
Not been unwell	269 (72)	225 (68)	1	*0.33*	1	*0.18*
Unwell, not hospitalised	63 (17)	71 (21)	1.35	0.91-2.04	1.46	0.97-2.21
Unwell and hospitalised	40 (11)	37 (11)	1.07	0.66-1.74	1.19	0.72-1.99
AUDIT score						
Audit Score ≤ 7	253 (68)	226 (68)	1	*0.85*	1	*0.73*
Audit Score ≥ 8	119 (32)	107 (32)	1.03	0.73-1.45	1.07	0.74-1.54

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model a priori including gender, community, age category as well as demographic/behavioural factors which were associated with case/control status (i.e. whether CHiP was known to participant prior to PopART to home-visit, whether HIV status has been disclosed, whether partner is HIV positive and on ART, and lifetime number of sexual partners)
4. One participant (control) with missing gender data
5. Previously married = separated/divorced/widowed
6. p-value for test for tend
7. Principal components analysis
8. HH factors detailed house structure, water, sanitation, electricity and cooking fuel used; assets listed were: working cell-phone, bicycle, motorcycle or scooter, car/bakkie, electricity to house, television set, fridge/freezer, radio, computer/laptop, CD or MP3 player, stereo/cassette/other music player, "none of the above"
9. Participant's own definition of "main partner"

Table 6.2: Participants perceptions of HIV service factors which may affect initiation of timely treatment

	Controls (Achieved TLA) N (%)	Cases (Did not achieve TLA) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value,* 95 % Confidence Interval
CHiP related factors						
Was the CHiP previously known to participant (prior to PopART home-visit)						
N	259 (70)	253 (76)	**1**	***0.05***	**1**	***0.006***
Y	113 (30)	80 (24)	**0.70**	**0.48-1.01**	**0.58**	**0.39-0.86**
Did participant have an HIV test with CHiP [4]						
N	47 (13)	27 (8)	1	*0.05*	1	*0.07*
Y	325 (87)	306 (92)	1.63	0.99-2.71	1.60	0.95-2.70
Was the CHiP someone you could talk to openly? [5]						p_{trend} [6] *0.01*
Strongly disagree/Disagree	7 (2)	14 (4)	1	***0.02***	1	***0.04***
Agree	66 (18)	80 (24)	0.59	0.22-1.58	0.64	0.23-1.81
Strongly agree	299 (80)	239 (72)	**0.37**	**0.14-0.97**	0.41	0.15-1.13
Factors specifically affecting linkage to care						
Time constraints affecting linkage to care						
Already in care/ time not a constraint for LTC	289 (78)	231 (69)	**1**	***0.02***	**1**	***0.02***
Time constraints due to livelihood/housework or both	82 (22)	102 (31)	**1.62**	**1.14-2.30**	**1.64**	**1.14-2.38**
Among those never previously registered for care prior to CHiP referral (N=603), did the following affect linkage to care?						
"Clinic is only open when I am at work"						
N	262 (85)	231 (78)	**1**	***0.03***	**1**	***0.02***
Y	46 (15)	64 (22)	**1.63**	**1.06-2.51**	**1.63**	**1.06-2.51**
"Clinic is too crowded"						
N	181 (59)	144 (49)	**1**	***0.12***	**1**	***0.006***
Y	127 (41)	151 (51)	**1.50**	**1.07-2.11**	**1.51**	**1.08-2.12**
"I could not go to the clinic because it is too far away/ because of the time it would take to travel there"						
N	299 (97)	273 (93)	**1**	***0.02***	**1**	***0.03***
Y	9 (3)	22 (7)	**2.52**	**1.13-5.61**	**2.55**	**1.14-5.69**
"I am not ready to go the clinic for HIV care"						
N	249 (81)	183 (62)	**1**	***<0.001***	**1**	***<0.001***
Y	59 (19)	112 (38)	**2.68**	**1.84-3.89**	**2.75**	**1.89-4.01**
"I will only go if/when I feel sick"						
N	270 (88)	232 (79)	**1**	***0.003***	**1**	**0.02**
Y	38 (12)	63 (21)	**1.96**	**1.26-3.07**	**2.00**	**1.27-3.14**

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model a priori including gender, community, age category as well as demographic/behavioural factors which were associated with case/control status (i.e. whether CHiP was known to participant prior to PopART to home-visit, whether HIV status has been disclosed, whether partner is HIV positive and on ART, and lifetime number of sexual partners)
4. Participants who did not have a test with CHiPs were those who self-reported known HIV-positive status, while those who had an HIV test with CHiPs were likely to be previously undiagnosed.

Table 6.3: Participants' perceptions of advantages and disadvantages of initiation of timely treatment

	Controls (Achieved TLA) N (%)	Cases (Did not achieve TLA) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value*, 95 % Confidence Interval
Individual level factors encouraging initiation of timely treatment ("Did any of the following encourage you start ART?")						
"For my health - even though I don't feel unwell"						
N	96 (26)	127 (38)	**1**	***<0.001***	**1**	***<0.001***
Y	275 (74)	206 (62)	**0.54**	**0.39-0.75**	**0.53**	**0.38-0.75**
Recommended by HCW (CHiP/clinic staff)						
N	35 (9)	55 (17)	**1**	***0.005***	**1**	***0.02***
Y	336 (91)	278 (83)	**0.52**	**0.33-0.82**	**0.56**	**0.34-0.91**
To protect partner from getting HIV						
N	189 (51)	188 (56)	1	0.11	1	0.19
Y	182 (49)	145 (44)	0.78	0.58-1.06	0.81	0.58-1.12
"I know someone/others who are well on ART and want to be on it too"						
N	142 (38)	155 (47)	**1**	***0.01***	1	*0.08*
Y	229 (62)	178 (53)	**0.67**	**0.48-0.92**	0.74	0.53-1.03
Individual level factors discouraging initiation of timely treatment ("Did any of the following discourage you from starting ART?")						
"I was worried someone would find out about my HIV because of taking treatment/going to the clinic"						
N	278 (75)	232 (70)	1	*0.1*	1	*0.15*
Y	93 (25)	101 (30)	1.33	0.95-1.86	1.30	0.91-1.87
"I was/am not ready to take ART"						
N	285 (77)	196 (59)	**1**	***<0.001***	**1**	***<0.001***
Y	86 (23)	137 (41)	**2.42**	**1.73-3.38**	**2.25**	**1.58-3.21**
"I don't think the treatment works so there is no point in starting"						
N	333 (90)	285 (86)	1	*0.12*	1	*0.16*
Y	38 (10)	48 (14)	1.44	0.91-2.29	1.42	0.87-2.30
"I don't like the idea of taking life-long treatment"						
N	288 (78)	234 (70)	**1**	***0.03***	**1**	***0.05***
Y	83 (22)	99 (30)	**1.48**	**1.04-2.09**	**1.44**	**1.00-2.07**
Stigmatising attitudes which may affect initiation of timely treatment						
"People living with or thought to be living with HIV are verbally insulted, harassed and/or threatened"						p_{trend} [5] *0.27*
Strongly disagree	46 (12)	34 (10)	1	*0.17*	1	*0.08*
Disagree	76 (20)	83 (25)	1.47	0.85-2.53	1.64	0.92-2.92
Agree	137 (37)	133 (40)	1.28	0.76-2.15	1. 30	0.76-2.23
Strongly agree	113 (30)	83 (25)	0.95	0.55-1.63	0.95	0.54-1.66
"I have felt ashamed because of my HIV status"						***p_{trend} [5] 0.007***
Strongly disagree	118 (32)	86 (26)	1	*0.02*	1	***0.05***
Disagree	139 (37)	106 (32)	1. 10	0.74-1.64	1. 20	0.78-1.84
Agree	59 (16)	74 (22)	**1.83**	**1.12-2.98**	**1.82**	**1.10-3.03**
Strongly agree	56 (15)	67 (20)	**1. 70**	**1.06-2.72**	**1.71**	**1.05-2.79**
"I have been excluded from social gatherings or activities because I have HIV"						p_{trend} [5] *0.16*
Strongly disagree	162 (44)	134 (40)	1	*0.73*	1	*0.30*
Disagree	187 (50)	177 (53)	1.14	0.82-1.59	1.31	0.94-1.89
Strongly agree/ agree	23 (6)	22 (7)	1.13	0.59-2.16	1. 40	0.71-2.76

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model a priori including gender, community, age category as well as demographic/behavioural factors which were associated with case/control status (i.e. whether CHiP was known to participant prior to PopART to home-

visit, whether HIV status has been disclosed, whether partner is HIV positive and on ART, and lifetime number of sexual partners)

4. There were very few responses in the “strongly agree” and “agree” categories for this question, responses are therefore grouped as shown to be more meaningful/increase power
5. p-value for test for trend

Supplementary Table 6.1: Factors with effect modification by gender, of association with case/control status

	Controls (Achieved TLA) N (%)	Cases (Did not achieve TLA) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value,* 95 % Confidence Interval	Controls (Achieved TLA) N (%)	Cases (Did not achieve TLA) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio[3]	*LRT [2] p-value,* 95 % Confidence Interval
	Men						Women					
Demographic, sexual behaviour and health related characteristics of cases and controls												
Educational attainment												***p_{em} [4] 0.005***
Primary (Grade 0-7)	70 (46)	45 (34)	**1**	***0.06***	**1**	***0.02***	113 (51)	108 (54)	1	*0.30*	1	*0.21*
Junior secondary (Grade 8-9)	36 (24)	45 (34)	**2.04**	**1.13-3.67**	**2.50**	**1.30-4.82**	58 (26)	39 (19)	0.74	0.45-1.23	0.71	0.41-1.24
Senior secondary (Grade 10-12) or higher education	45 (30)	42 (32)	1.41	0.79-2.52	1.81	0.94-3.50	49 (22)	54 (27)	1.16	0.68-1.97	1.21	0.68-2.17
Was the CHiP known to the participant prior to offer of HBT?												***p_{em} [4] 0.006***
N	106 (70)	112 (85)	**1**	***0.006***	**1**	***<0.001***	153 (69)	141 (70)	1	*0.68*	1	*0.38*
Y	45 (30)	20 (15)	**0.41**	**0.22-0.77**	**0.29**	**0.14-0.58**	68 (31)	60 (30)	0.90	0.57-1.44	0.80	0.49-1.32
Have you disclosed your HIV status to anyone?												***p_{em} [4] 0.002***
N	24 (16)	27 (20)	1	*0.27*	1	*0.35*	14 (6)	47 (23)	**1**	***<0.001***	**1**	***<0.001***
Y	127 (84)	105 (78)	0.70	0.38-1.31	0.72	0.37-1.43	207 (94)	154 (77)	**0.20**	**0.11-0.39**	**0.18**	**0.09-0.36**
AUDIT Score												***p_{em} [4] 0.02***
Audit Score 7 or lower	82 (54)	58 (44)	**1**	***0.05***	**1**	***0.009***	171 (77)	168 (84)	1	*0.07*	1	*0.08*
Audit Score 8 or higher (hazardous and harmful alcohol use; possible dependence)	69 (46)	74 (56)	**1.64**	**1.00-2.70**	**2.13**	**1.20-3.81**	50 (23)	33 (16)	0.63	0.38-1.04	0.61	0.35-1.06
Participants perceptions of HIV service factors which may affect initiation of timely treatment												
Time constraints affecting linkage to care												***p_{em} [4] 0.03***
Already in care/ time not a constraint for LTC	96 (64)	82 (62)	1	*0.91*	1	*0.86*	193 (87)	149 (74)	**1**	***<0.001***	**1**	***0.001***
Time constraints due to livelihood/housework or both	54 (36)	50 (38)	1.02	0.63-1.69	1.05	0.61-1.81	28 (13)	52 (26)	**2.43**	**1.44-4.10**	**2.47**	**1.41-4.34**

Participants' perceptions of advantages and disadvantages of initiation of timely treatment												
I have felt ashamed because of my HIV status												***p_{em}[4] 0.02***
Strongly disagree	47 (31)	30 (23)	1	*0.002*	1	*<0.001*	71 (32)	56 (28)	1	*0.22*	1	*0.20*
Disagree	61 (40)	44 (33)	1.48	0.75-2.91	2.03	0.93-4.42	78 (35)	62 (31)	0.96	0.58-1.61	1.02	0.58-1.77
Agree	17 (11)	35 (27)	4.84	2.06-11.39	6.57	2.59-16.67	42 (19)	39 (19)	1.08	0.58-2.02	0.98	0.50-1.91
Strongly agree	26 (17)	23 (17)	1.93	0.87-4.25	2.05	0.86-4.86	30 (14)	44 (22)	1.72	0.94-3.14	1.81	0.96-3.41
People sometimes talk badly about me because I am living with HIV												***p_{em}[4] 0.02***
Strongly disagree	27 (18)	33 (25)	1	*0.10*	1	*0.16*	56 (25)	45 (22)	1	*0.19*	1	*0.17*
Disagree	67 (44)	58 (44)	0.67	0.34-130	0.78	0.37-1.64	74 (33)	86 (43)	1.39	0.82-2.35	1.77	0.99-3.17
Agree	36 (24)	33 (25)	0.70	0.33-1.49	0.72	0.32-1.61	63 (29)	46 (23)	0.82	0.44-1.51	1.11	0.57-2.14
Strongly agree	21 (14)	8 (6)	0.28	0.10-3.05	0.30	0.10-0.89	28 (13)	24 (12)	0.93	0.46-1.86	1.31	0.62-2.75

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model a priori including gender, community, age category as well as demographic/behavioural factors which were associated with case/control status (i.e. whether CHiP was known to participant prior to PopART to home-visit, whether HIV status has been disclosed, whether partner is HIV positive and on ART, and lifetime number of sexual partners)
4. P value for effect modification by gender

Chapter 7: Discussion

Outline of chapter

This chapter will summarise and synthesise the findings of the four preceding chapters, with emphasis on the two case-control studies and discuss the implications of the PhD as a whole. Strengths and limitations will be examined and lessons learned will be presented. Recommendations will be made for further research. Finally, policy implications will be discussed.

Although this is a Discussion chapter, additional tables will be presented where necessary. Some data were not shown in the manuscripts which were written for publication of the studies (due to word limits and feasibility of what could be included in Tables), but are nonetheless of interest. They will therefore be presented in this chapter.

7.1 Research findings

The research undertaken for this PhD has explored the key steps in the cascade of HIV care, specifically applied to the context of the PopART trial. However, the findings of the nested studies should be broadly generalizable to many urban and peri-urban settings in sub-Saharan Africa where UTT may be delivered.

7.1.1 Home Based-HIV Testing and Counselling

The systematic review and meta-analysis on the uptake of HB-HTC systematically evaluated the published literature on the acceptability of HB-HTC as measured by HIV test uptake among those offered it at the household in sub-Saharan Africa between 2000 and 2012. The finding that 83% of those offered HB-HTC accepted it, at a time when PopART was still in the planning stages, was highly promising for the prospect of using HB-HTC as the main component to achieve universal testing in PopART. Evidence on the acceptability of HB-HTC has continued to emerge since then and has supported our results.(1-3)

The finding in our systematic review on HB-HTC that there were no significant differences between men and women in uptake among those offered HB-HTC highlights an important issue around the difference between uptake and coverage. Coverage measures acceptance out of all those estimated to be present (or living in the community for example), while if uptake is examined, the denominator is limited to those met and offered testing. This is important to bear in mind when examining data on HIV testing, so that uptake is not interpreted as equivalent to coverage. Uptake could be high but coverage would be low if not enough of a given population is encountered by service providers. Evidence indicates that there are fewer men found at home than women and HB-HTC providers may therefore encounter less men. (4, 5) Once contacted however, men are not notably less likely to accept HIV-testing.(4, 5) The challenge for achieving universal coverage, among men and women alike, lies in maximising the number of men contacted through HB-HTC. Weekend and evening

provision has been shown to increase the number of men encountered. (6, 7) This suggests that with innovative means to contact men, HB-HTC has the potential to have universal reach.

Having established that HB-HTC is broadly well accepted we wanted to establish if there were sub-sets of the population with particular demographic characteristics, behaviours or those holding certain views and beliefs that were being excluded / were not accepting HB-HTC despite being offered it at their doorstep (or because it was at their doorstep). Case-control study 1 was done to examine this question. By comparing a sub-set of the population who had been contacted and accepted HB-HTC (controls) with those who declined HB-HTC (cases) when offered it by the PopART CHiPs, we were able to explore differences in the two groups.

As described in Chapter 4, there were no fundamental differences in terms of demographic or behavioural characteristics between those who declined and those who accepted HB-HTC. The CC1 study sample was frequency matched by gender and community to ensure adequate representation of those groups. As such, rather than identify if there were any differences in uptake by gender (other PopART data on uptake of HB-HCT answer that) (4), we were able to explore differences between those who declined and those who accepted HB-HTC after accounting for gender. We were also able to examine if associations differed by the gender of the participant. Few other studies have been able to do this, with most having considerably fewer men in the study sample. (1, 8)

We observed no clear associations with case/control status according to age category. The association of HB-HTC uptake with age is conflicting, with some data indicating that older age groups are more likely to accept. (8) Age was therefore included as a potential confounding factor in the final multi-variable model given that it is generally recognised as an important determinant of engagement with health services.

Acceptors and non-acceptors of HB-HTC were similar in terms of educational attainment, employment and socio-economic position. Similarly, there were no differences by health status, health seeking behaviour or sexual behaviour and influences such as presence of other household members when offered HBT (Chapter 4, Table 4.1 and Table 7.1 below).

As described in Chapter 4, Table 4.1, most participants had lived in the community for 4 or more years, and this was associated with twice the odds of being a case i.e. having declined HB-HTC. This may be due to the fact that those who had lived in the community for some time were more likely to have been exposed to HIV-testing campaigns in the past and been tested before. Our data suggest that it was those who had never tested previously who were more likely to test (Chapter 4, Table 4.1). However in our study, those who had lived in the community for longer were neither more nor

less likely to self-report as not having previously tested (8% of those who had lived in the community for ≥4 years had not tested previously vs 5% of those who had lived in the community for ≤3 years; X2 p=0.26).

An alternative explanation might have been that those who were resident in the community for longer were more likely to be in stable partnerships and therefore considered themselves less at risk of HIV and declined HB-HTC as a result. Again, there is no suggestion of that in our data (no differences of lifetime number of sexual partners or self-perception of high risk sexual behaviour, by duration lived in community (Table 7.2)). Or it may be that participants who had lived in the community for 4 or more years were more traditional in their attitudes and therefore were more likely to have declined HB-HTC (after adjusting for age), although this is merely speculative.

There were differences observed by case/control status, with regard to perceptions about HIV care, treatment or service providers (Chapter 4, Table 4.3). Individuals who expressed favourable opinions about the CHiPs, about the convenience of testing at home and about accessing treatment without delay after diagnosis were more likely to accept HB-HTC. Participants who said that they knew people who had tested with the CHiPs were also less likely to decline HB-HCT and this likely ties in with a positive disposition towards the CHiPs, which encouraged testing. This suggests that the opinions shared between community members about HB-HCT provided by the CHiPs were positive rather than negative, therefore encouraging uptake of testing among those who knew others who had accepted CHiPs HB-HCT.

Participants who said that they were confident that they were HIV-negative or reported having recently tested (and were presumably also HIV-negative given that those who self-reported living with HIV were not routinely offered the HB-HCT intervention and would therefore not be part of the study sample), were more likely to decline HB-HCT. The fact that those who were previously test-naïve found HB-HCT acceptable when offered by the CHiPs is encouraging as it suggests HB-HCT is effective at increasing knowledge of HIV-status. As was described in Chapter 4, stigma and concerns about confidentiality were not associated with test uptake in our study. The implications of all these findings are discussed in section 7.4 below.

Table 7.1 Health seeking behaviour, circumcision (among men) and pregnancy (among women) status of cases and controls in CC1

	Cases (Non-acceptors) N (%)	Controls (Acceptors) N (%)	Odds Ratio [1]	*LRT [2] p-value*, 95 % Confidence Interval	Adjusted Odds Ratio [3]	*LRT [2] p-value*, 95 % Confidence Interval
Hospitalised in last 12m						
N	291 (93)	309 (94)	1	*0.65*	1	*0.54*
Y	21 (7)	20 (6)	1.16	0.61-2.22	1.23	0.64-2.36
Ever circumcised (among men)						
N	94 (62)	85 (57)	1	*0.52*	1	*0.59*
Y	58 (38)	64 (43)	0.84	0.50-1.42	0.86	0.51-1.47
Ever pregnant (among women)						
N	29 (18)	31 (17)	1	*0.76*	1	*0.79*
Y	279 (82)	148 (83)	0.91	0.50-1.65	0.98	0.49-1.98

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model including gender, community, age category and years lived in the community
4. P value for test for trend

Table 7.2 Sexual behaviour of CC1 participants by duration lived in the community

Years lived in the community	≤3 N (%)	≥4 N (%)
No of lifetime sexual partners		
1	29 (32)	136 (28)
2	16 (18)	98 (20)
3	24 (27)	148 (30)
≥ 5	21 (23)	112 (23)
My sexual behaviour has put me at risk of HIV		
N	78 (81)	436 (81)
Y	18 (19)	102 (19)

7.1.2 Timely linkage-to-care and ART initiation without delay

Our systematic review on the cascade-of-care following community-based detection of HIV described in Chapter 5 established that there is considerable variability in the existing literature when it comes to measures of reporting linkage-to-care and ART initiation and in outcomes reported, even for similar time periods. Nonetheless, the evidence from some of the studies with high proportions LTC and/or initiated ART following home or other community location-based HTC suggests that it is possible to achieve favourable outcomes. (9-11)

We also found evidence to suggest that individuals who had been diagnosed previously were more likely to link-to-care than those who reported being newly diagnosed. This could be because those who had been previously diagnosed had previously linked-to-care and even if they had defaulted from care, were less daunted by the prospect of linking again. Alternatively, it may that PLWH need time to come to terms with an HIV diagnosis and once there is greater acceptance of living with HIV,

individuals feel able to engage with services. PopART intervention data and evidence from the ANRS TasP trial which indicate that there is incremental linkage-to-care over time since referral support this idea. (4, 5)

Our systematic review did not find any benefit from using point-of-care CD4-count testing with regard to linkage-to-care/ART initiation outcomes following home or other community location-based HTC. This is in contrast to studies based in facilities, where CD4-count testing provided an incentive for individuals who test HIV positive to register for HIV care. (12) However, these findings have to be interpreted with caution given the variability in the measures used in the studies which reported on LTC/ART initiation following community-based HTC which met inclusion criteria for the systematic review. Nonetheless, from the available evidence we did not find differences between different modes of community-based HTC e.g. mobile vs home-based testing, for instance.

In Case-control study 2 we focused on timely linkage-to-care and ART initiation within 6 months (referred to as timely linkage-to-ART), irrespective of CD4-count or immune-status. The study was done in PopART Arm A communities where universal test and treat was provided, to compare those who had achieved TLA (controls) with those who had not (cases). Just as in CC1, CC2 was designed so that participants from all relevant communities and both genders would be represented in the study. And as with CC1, CC2 found no differences in terms of demographic characteristics between those who achieved TLA and those who did not.

However, there were some behavioural characteristics related to self-reported sexual behaviour and disclosure of HIV which were predictive of case/control status. As previously seen (Chapter 6, Table 6.1) there is a suggestion that the more lifetime sexual partners participants reported, the more likely they were to achieve TLA (reduced odds ratios of being a case). This might be due to the fact that those who had had a greater number of sexual partners were more accepting of living with HIV (as opposed to being in disbelief/denial about their diagnosis if they considered themselves at low risk of getting HIV, for example).

Disclosure of HIV status was seen to encourage TLA and our data suggest a similar encouraging effect from having an HIV-positive partner on ART (the latter however not reaching statistical significance in the multi-variable adjusted model). In contrast, reporting an HIV-positive partner who was not known to be on ART meant that the individual was twice as likely to have failed to achieve TLA, compared to the baseline group consisting of individuals who did not report having an HIV-positive partner (i.e. partner reportedly HIV-negative or status unknown, or no partner in last 12 months). Collectively, these findings could suggest that participants who had come to terms with

their HIV diagnosis and were in relationships where openness about HIV related matters prevailed, had an advantage with regards to achieving TLA.

As was seen in CC1, participants who reported favourable views about the CHiPs – for instance strongly agreeing that the CHiP was someone they could talk to openly - were more like to achieve TLA (Chapter 6, Table 6.2). We also saw that participants who were in favour of treatment (encouraged to start treatment "for my own health even though I don't feel unwell" or "I know someone/others who are well on ART and want to be on it too") were more likely to achieve TLA whereas those with more negative views ("I was/am not ready to take ART" or "I don't like the idea of lifelong treatment") were more likely to fail to achieve TLA (Chapter 6, Table 6.3). Encouragingly, knowing others on treatment and previously knowing the CHiP were predictive of achieving TLA.

As has been demonstrated by others, participants who reported time constraints were more likely to fail to achieve to TLA (Chapter 6, Table 6.2). (13) Similarly, among those who had never previously registered for care, time-related constraints to accessing the clinics were seen to be barriers to TLA. Further, clinic infra-structure factors including opening hours and crowding in the clinic were predictive of failure to achieve TLA. Of note, health care worker (HCW) factors (being treated badly by HCWs or inadvertent disclosure by HCW) - were not associated with TLA (Table 7.3). In fact, participants who said the recommendation of a HCW to start ART was an encouraging factor for TLA, were more likely to succeed with timely initiation (Chapter 6, Table 6.3).

Table 7.3: Health care worker related perceptions held by participants

	Controls (Acceptors) N (%)	**Cases (Non-acceptors) N (%)**	**Odds Ratio [1]**	***LRT [2] p-value*, 95 % Confidence Interval**	**Adjust-ed Odds Ratio[3]**	***LRT [2] p-value*, 95 % Confidence Interval**
I think people get treated badly by clinic staff if they are HIV+ve						
N	272 (88)	254 (86)	1	*0.48*	1	*0.19*
Y	36 (12)	41 (14)	1.19	0.73-1.95	1.41	0.84-2.37
"A health worker may disclose to others without my permission that I am on treatment for HIV (if I am on treatment)"						p_{trend} [5] *0.15*
Strongly disagree	182 (49)	163 (49)	1	*0.28*	1	*0.23*
Disagree	169 (45)	141 (42)	0.93	0.68-1.27	0.99	0.70-1.39
Strongly agree/ agree	21 (6)	29 (9)	1.52	0.83-2.78	1.7	0.90-3.20

1. A priori adjusted for gender and community to reflect sampling strategy
2. Likelihood ratio test
3. Multivariable model a priori including gender, community, age category as well as demographic/behavioural factors which were associated with case/control status (i.e. whether CHiP was known to participant prior to PopART to home-visit, whether HIV status has been disclosed, whether partner is HIV positive and on ART, and lifetime number of sexual partners)
4. There were very few responses in the "strongly agree" and "agree" categories for this question, responses are therefore grouped as shown to be more meaningful/increase power
5. p-value for test for trend

As for uptake of HB-HTC, stigmatising attitudes do not appear to be major determinants for engagement with services. The implications of the findings from CC2 are discussed in section 7.4 below.

7.2 Limitations and strengths of research conducted for PhD

7.2.1 Potential limitations of study design and procedures and findings

7.2.1.2 Study design

During the planning stages of PopART and the nested case-control studies, it was anticipated that non-uptake of the HB-HTC and the timely treatment interventions would be infrequent. As such, a case-control design was chosen with the assumption that the "non-engagers" (with the unsuccessful outcome) would befit being the cases, and a sample of controls who accepted the interventions (i.e. with the successful outcome) could be chosen to represent the population from which the cases arose, for comparison.

As PopART intervention data has emerged, it has become clear that initiation of timely treatment - within 6 months for example - has not been as successful as initially hoped. (4) PLWH initiate treatment and increasingly so with time since referral, but achieving timely linkage and treatment initiation has been a challenge. As such, for CC2 in some communities there were fewer controls (achieved TLA) than cases (delayed ART initiation or not started at all – at the time of random selection for CC2). The frequency matching was therefore not always 1 case: 1 control per community. However, at the analysis stage odds ratios were adjusted for community and any imbalances would therefore be accounted for.

The case-control design meant that specific individuals who were randomly selected for having a specific outcome (case or control) had to be traced in order to ask permission for study participation. As already described in Chapter 4 and 6 for CC1 and CC2 respectively, tracing of named individuals who were previously encountered in the community by the CHiPs at the time of intervention delivery was not always possible. Despite prior knowledge of the communities, the extent of mobility and frequency of turnover of addresses was greater than expected. Given the importance in case-control studies of selecting individuals with known outcomes and in specified proportions for the required case: control ratio, the difficulty in tracing community members became a key challenge for both studies.

Related to the above observation in PopART intervention data that PLWH took longer than we had initially hoped to start ART, the case/control definition in CC2 had to be modified as described in Chapter 6. Initially, treatment initiation irrespective of CD4-count within 3 months was hoped for to maximise the impact of treatment as prevention by minimising the duration of uncontrolled viraemia in a given PLWH who was not yet on treatment. However, the time-period had to be extended to 6 months to allow more individuals to meet the control criteria of initiating treatment within a given (relatively short) period. PopART intervention data indicate that 42% of PLWH who were referred by CHiPs had initiated ART by six months, representing the vast majority of those who did so within the first year. Therefore, on balance 6 months was chosen as the most meaningful time period to use as a cut-off for the definition of "timely" initiation of ART. A shorter time would be applicable to too few individuals and a longer period would not have the full benefit of treatment as prevention.

7.2.1.3 Recruitment of cases and selection bias

The CC studies sought to explore reasons for non-uptake of PopART interventions and it is possible that a substantial proportion of those individuals who declined HB-HTC / did not achieve TLA, also declined study participation. As shown in Chapter 4 and 6, there were losses of individuals initially identified as potential candidates for the study. This could mean that the individuals who were encountered were not necessarily representative of all those who were offered interventions. In CC1 there was no evidence of differential recruitment based on outcome as shown in Chapter 4, Figure 2. In CC2, individuals who were not traceable for follow-up with a resultant "unknown" ART uptake status were not eligible to participate in the study. As a result, there may be a selection bias related to who was eligible for study participation, especially as it is reasonable to assume that household members who were absent at multiple follow-up attempts, may also have been more likely not to have initiated timely ART. Among those eligible, the failure to locate individuals and/or the refusal to participate in the case-control study (i.e. response rates) were differentially associated with success of achieving TLA – a lower proportion of randomly selected potential cases were located and recruited than among potential controls (Chapter 6, Figure 2). While undesirable, this limitation in CC2 was somewhat inevitable given the study question and the necessary pre-requisite of individuals' willingness and consent to participate.

The most important short-coming of the case-control studies was that only community members who had accepted the intervention when offered by CHiPs i.e. agreed to have their identification details recorded and partook in the CHiP household visit (which included the offer of HB-HTC and referral for HIV care for those identified as HIV-positive), could be eligible for random selection into the case-control studies. This means that those who refused outright to have any form of

engagement with the CHiPs are not represented in the case-control studies at all. There is a reasonable chance that those individuals are systematically different from those who accepted the intervention. Therefore, the case-control study findings can only be generalised to the latter group and not all community members. However, that was the goal from the outset i.e. to explore the factors associated with uptake of interventions among those who were offered them. Furthermore, estimates suggest that it is a relatively small proportion of community members (especially among women) who did not participate in the intervention. Data from the first year of PopART in Zambia indicate that among women, 90% of those enumerated consented to the PopART intervention and while the proportion among men was smaller at 77%, it was still the majority of men in the community. (4)

7.2.1.4 Information bias

Information bias in both CC studies may have resulted either from the respondents (recall or reporting (e.g. social desirability) bias) or from the researcher (observation bias). Recall could have been a problem in both studies given that the CC studies were conducted towards the end of the intervention annual round for feasibility reasons. It is therefore possible that participants' responses were representative of their situation/views/perspectives at the time of the study but that these were changed from the time of the intervention. For example, in CC1 factors associated with acceptance of HB-HTC at the time of offer by CHiPs were the focus of the study, yet the participants' responses may have been reflective of factors at the time of the CC study conduct instead. For some participants who were included in the intervention at the start of the annual round, the CC study would have been conducted approximately a year later. For the majority however, there would have been a shorter time lag between being offered HB-HTC and taking part in the study. Also, given the importance of giving everyone who participated in the intervention during the first year an equal probability of being included in the study, the random selection and therefore the study had to occur after completion of the first annual round of the intervention (or as close to it as possible).

The questionnaires were dependent on self-report and would inevitably have been influenced by individual subjectivity. For instance, how participants responded to the question about the number of years lived in the community may have been inconsistent if for example, there were periods of out-migration or having returned to a village of origin for an extended period to care for a relative, as often happens in these communities. Depending on the participant's interpretation of the question, they may have given the duration as the entire time since first moving into the community, or alternatively may consider their most recent return to the community as the starting point to calculate duration.

Another factor to consider was the fact that both cases and controls were asked identical questions – in order to allow comparisons between the two groups, even though some questions would have involved hypothetical scenarios for some participants. This is a nuanced concept which may have been difficult for some participants to grasp. For example, cases in CC1 (who would have declined HB-HTC), were asked about reasons which may have encouraged them to accept. This was done to allow comparison with controls who did accept HB-HTC, regarding factors associated with motivation to test. It is possible that those who declined simply said "No" when asked about any factor which encouraged uptake. As seen in chapter 4, Table 4.3 and chapter 6, Table 6.3, this does not appear to be an overwhelming concern but it remains a potential consideration.

Social desirability bias is a concern when interpreting self-reported data. However, given that there were no a priori hypotheses about the associations of the exposure variables and the outcomes, it is not expected that any bias would have been differential and the conclusions drawn as a result were more likely to under-estimate rather than over-estimate associations.

Further, field researchers were kept blind to case vs control status of study participants until the end of the questionnaire to minimise the observer bias which could have arisen from prior knowledge of whether a given participant was an acceptor or non-acceptor of the intervention.

7.2.1.5 Reverse causality

Given the case-control design and the fact that the outcome had occurred before the study was conducted, reverse causality is the other potential limitation when interpreting certain factors in both studies. To illustrate the point using CC2 and a question related to whether participants were worried that a HCW may disclose their HIV status without their permission – participants who had achieved TLA may have formed their opinions about HCWs after attending the clinic. Positive views expressed about them may be reflective of the experience in the clinics after achieving the outcome. In other words, in this example the "predictor" we were examining arose after the outcome. Therefore, to conclude that the positive views about health care workers encouraged those PLWH to link to care and start ART would be wrong. This is one of the key reasons that the findings of our studies are limited to observations of association and causality cannot be inferred. Reverse causality applies more to certain factors such as opinions and perceptions, which are changeable and have less objective measures, than others such as demographic characteristics.

7.2.2 Strengths of research conducted

The research conducted to contribute to this PhD also had several strengths. The case-control studies are nested within the largest HIV prevention trial to date in two high HIV prevalence countries in sub-Saharan Africa. The communities represented in the studies have an average total

population size of approximately 55,000 individuals (ranging from 20,000 to 150,000). All the PopART study sites are urban or semi-urban and this is a key strength given that in sub-Saharan Africa prevalence of HIV in urban settings is twice that of rural areas and a growing proportion of people live in urban areas. (14) This, along with the fact that the populations studied come from more than one country, add to the generalisability of the findings.

Despite the limitations described above, the fact that the case-control study populations were randomly selected from communities which were randomly allocated to receive the universal testing and universal treatment intervention is a further advantage. There is only one other quantitative study exploring a limited number of factors associated with uptake of HB-HTC (1) and one on the factors associated with ART initiation (15) in the context of UTT. We examined a wide range of themes to a level of depth that others have not in existing published literature – especially when the background context of universal test and treat is considered.

The study samples were also of substantial size with over six and seven hundred participants (CC1 and CC2, respectively). Despite falling short of the originally intended sample sizes (described in Chapter 2, Section 2.5) we still had approximately 80% study power to detect associations with odds ratios of ~1.75 or higher (or ~0.5 or lower), for explanatory variables with 15% prevalence among controls ($\alpha = 0.05$). At this level, important differences which would have a population level impact would be detected by the studies, even if weaker associations of less common factors may have been missed.

In addition to the research conducted for the CC studies, the findings of two systematic reviews done as part of the PhD make important contributions to the understanding of HB-HTC and TLA in sub-Saharan Africa. The systematic review and meta-analysis on HB-HTC which was published in 2012 has promoted the acceptability of home-based testing as a means to increasing knowledge of HIV status in high prevalence settings. The second systematic review on the cascade of care after HIV diagnosis in the community (which is under review for publication) provides detailed scrutiny of the published literature and highlights the importance of consistency in reported data if we are to measure progress against UNAIDS 90-90-90 targets.

7.3 Lessons learned from PhD process

The period since embarking on the PhD has been a time of intensive learning and reflection. The first lesson learned was the need for flexibility and patience when conducting research. Given that the nested case-control studies were nested within a very large trial such as PopART there were a number of delays incurred by the main trial which affected sub-studies. The reasons ranged from delays in obtaining approvals from local regulatory authorities and greater than anticipated time

required to conduct training of field staff. The result was that the main trial started up to a year later than initially anticipated. This had a direct impact on when the case-control studies could start. Subsequent changes to PopART staffing arrangements also meant that new staff had to be recruited to work on the case-control studies, which required further preparation and training.

The next major lesson learned arose from the data irregularity issue in South Africa, described in Chapter 2, Section 2.4.2. The episode was challenging in terms of the ethical considerations of what would be the best course of action to take. The greatest dilemma was in terms of seeking to retain data which were provided by participants in good faith and collected correctly, versus ensuring that data which were compromised were appropriately excluded. Further, the event exposed some of the difficulties which arise from collaborations with partner institutions which may have different perspectives and priorities.

The key lessons learned from the episode for better research practice in future included the following. Frequent but open communication with field staff is required to understand challenges they face. In this case, staff were fearful to report that a number of participants who were randomly selected to be approached for case-control study participation were in reality impossible to find - given the feedback from neighbours or other household members that no one fitting the names/age of the participants sought were ever known at the given addresses. This could have resulted in extreme frustration for the case-control study staff who then felt that fabricating data on non-existent individuals was the preferred course of action, rather than being seen to be ineffective at recruiting participants. There were implications for those staff in terms of future employment in the PopART trial (upon the completion of the case-control studies) which may have acted as perverse incentives for data fabrication.

Understanding the obstacles staff are facing can improve how we support and manage them and what we expect of them. Greater anticipation of potential difficulties may have enabled clearer guidance for field level researchers and managers, so that they could have been better prepared in turn. Another vital lesson learned is the value of using electronic data-capture without which there would have been far fewer checks available to be able to explore and investigate irregularities in the data. As a result of careful monitoring of the data in “real-time”, I was able to detect the irregularities which arose in South Africa during CC1. The main trial has also learned from the experience and systems of data monitoring have been instituted as a result, with “red flags” raised when performance becomes implausibly high, for instance.

Insights have also been gained into the subtleties of questionnaire design, in particular the need to balance questions which are detailed enough to elicit important information against excessive detail which leads to participant and/or field researcher fatigue and resultant meaningless responses being recorded. Given the challenges faced in participant recruitment posed by the mobility and frequent in- / out-migration of community members, another lesson learned is the importance of having enough background information about study settings and the social dynamics at play before studies are planned, if possible.

7.4 Research in context, implications of the findings and recommendations for the future

The research for this PhD set out to establish whether the PopART UTT intervention would be acceptable across communities. It was conducted within the context of universal testing (CC1 on HB-HTC) and universal test and treat (CC2 on TLA) and indicates that the interventions do not systematically exclude any subsets of the population. Our research provides supportive evidence for the potential to achieve universal coverage, in similar urban high-HIV prevalence settings in sub-Saharan Africa.

The importance of making the distinction between uptake of HB-HTC and coverage has been highlighted earlier. We have shown that HB-HTC is highly acceptable and does not exclude individuals by demographic or behavioural characteristics. The key to achieving universal access to testing using HB-HTC, will however, require innovative means to ensure that those who may not spend as much time at home (e.g.. men and young people in general) have the opportunity to be offered HB-HTC. Weekend and evening provision of services is one solution (6,7) but there may be limits to what is feasible. Concerns about staff safety (with respect to going door-to-door in the evenings), employment law (weekend working may be problematic in some settings) and recruiting staff to work unsociable hours (including the cost of paying out-of-hours salary rates), may all be obstacles.

We have examined HB-HTC delivered by lay health workers, but the use of self-testing in the home with the subsequent support of lay health workers in the community to help interpret results and facilitate TLA has also been explored. (16) More research is needed on whether it may be the answer to reaching those who are less frequently encountered at home by staff going door-to-door. Iwuji et al from the ANRS TasP trial have suggested that supplementing HB-HTC with mobile-HTC in community locations may be the answer to help reach those who are missed or who chose not to participate in HB-HTC interventions, in order to reach universal coverage. (1) The SEARCH trial for

instance, is using multi-disease health campaigns in the community in combination with HB-HTC to maximise their coverage. (6)

HIV testing is the gateway to HIV care for PLWH and can help HIV-negative individuals to remain so. (17) It appears from our research that HB-HTC is effective in reaching those who had not previously tested for HIV, which is key to increasing knowledge of HIV status. However, an individual's HIV status may change over time and therefore on-going knowledge of HIV-status is essential. This requires repeat testing at regular intervals. Data from CC1 indicate that individuals weigh-up their own risk when deciding whether an HIV test is relevant for them. Those who believe that they are likely to be HIV-negative appear to decline (or perhaps defer) testing on the basis that there is "no need" to test for their circumstances. This finding was also reported by Iwuji et al from the ANRS TasP trial.(1) WHO no longer recommends repeat testing to cover a window-period (18) and for a given individual it is logical that an HIV-negative result would indicate there is no need for further testing if sexual partnership circumstances remain unchanged, assuming they are in a sero-concordant HIV-negative relationship. Interestingly, those who agreed with the statement "My sexual behaviour has put me at risk of HIV" were more likely to accept HB-HTC. Interpreted together with the finding above about those who considered themselves likely to be HIV negative, it seems that community members are doing their own risk assessments about the added value of accepting HIV testing for their own perceived circumstances. This seems a perfectly reasonable position – provided the assessment of risk is based on an accurate picture of potential exposure to HIV.

However, from a public health perspective an HIV-negative result may be false re-assurance given that HIV transmission is embedded not only within individual sexual partnerships but sexual networks. Any given individual may be unwittingly exposed to (new) risk if their partner's circumstances change or are not what they believe them to be. With this in mind it seems important from a public health point of view that repeat on-going testing at fairly regular intervals (e.g. annually) is recommended in settings where HIV-prevalence is high. In order to achieve this, individual community members will have to be convinced that having an HIV test which is freely available and convenient is worth accepting irrespective of perceived risk. Self-testing using oral test kits could have a particular role for this.

Evidence from CC2 suggests that those who perceive that their sexual behaviour has put them at risk of HIV were more likely to achieve TLA. More research is needed on how to effectively tailor public-health messaging to address the issue of self-risk assessment and engagement with services, not least because the issues to be considered involve intimate relationships and they touch on sensitive societal norms and values relating to sexual behaviour. Social science research on the interplay

between perceived sexual risk and decision making pathways about accessing care could help enhance engagement with HIV prevention services and make an important contribution towards achieving universal coverage.

Data from more than one HIV prevention trial which are seeking to reduce HIV incidence using treatment as prevention indicate that linkage to care is the current most important barrier to universal treatment. (4, 19) As discussed in Chapter 6, factors which were seen to affect TLA in CC2 could have done so by influencing either or both, linkage to care and/or ART initiation. We observed that the CHiPs had a positive influence with respect to encouraging engagement with services. While social desirability bias may have influenced how commonly our study participants reported a positive view of the CHiPs, it seems unlikely it would have been differentially associated with case/control status. The association of a positive view of the CHiPs with engagement with services (uptake of HB-HTC or achieving TLA) therefore, seems significant. Evidence from other studies which have used lay health workers to enhance linkage to care have also seen benefits to outcomes.(9-11)

Our findings from CC1 indicate that knowing someone else who accepted HB-HTC from CHiPs was associated with acceptance of HB-HTC. This suggests that the more coverage is achieved the greater uptake could become. Similarly, the data from CC2 suggest that we have reason to be optimistic that the acceptability of the universal treatment intervention in PopART (as defined by TLA) will improve over time. This is evidenced by the fact that knowing others on treatment and previously knowing the CHiP were predictive of achieving TLA. Relatedly, we also found that not only is disclosure of HIV-positive status associated with TLA as has been seen by others (15), but also that participants who reported that they had an HIV-positive partner on ART were more likely to succeed with TLA themselves. Overall, this is promising for future years of PopART implementation as it could mean that positive momentum will build over time as more of the community become familiar with the PopART interventions and services provided by CHiPs.

It has long been acknowledged that health-facilities pose a barrier to linkage to care and ART initiation. (13) Our research findings help unpick the underlying factors which contribute to this. While clinic infra-structure factors (over-crowding, clinic opening hours etc.) were barriers to TLA, a positive view of health care workers seems to encourage TLA (Chapter 6, Tables 6.2 and 6.3). This information is helpful when looking at which components pose barriers to linkage to care to make improvements in delivery of ART. Community ART clinics and community groups for drug refills which are led by HCWs in the community, make the most of the benefits of HCWs but remove the barriers posed by needing to attend clinics. (20) The potential role of CHiP led community models of ART delivery within PopART is being explored in an ancillary study.

Currently, community health workers hold a relatively low status in the hierarchy of health care workers. Our findings support the idea that we should invest in the CHiPs and similar lay health workers as a cadre of staff. Training and support on areas related to motivational interviewing or similar counselling skills should be considered to capitalise on their apparent ability not only to deliver the HB-HTC but to increase uptake and encourage TLA, seen in our studies.

We did however also find that protecting a partner from acquiring HIV as a reason to start ART was not associated with increased TLA (Chapter 6, Table 6.3), and this suggests that greater efforts to promote a "treatment for prevention" message are indicated.

Both CC studies found that stigma was not an important barrier to uptake of PopART interventions, suggesting progress in attitudes related to HIV given that over the years the opposite has been reported. (13) Similarly, fear of lack of confidentiality of testing for HIV at home was not a barrier to uptake of HB-HTC. Taken together, these findings reflect the advances which have been made in addressing HIV in SSA.

7.5 Conclusion

In conclusion, the research done for this PhD adds to current knowledge on the cascade of care in the context of UTT. While there are limitations to consider, the data provide in-depth information on the factors associated with the uptake of key interventions in the PopART model of UTT, therefore fulfilling the aim of the PhD. The findings of few differences by demographic and behavioural characteristics between those who accepted and those who did not accept PopART interventions suggest acceptability across population sub-groups. This holds great promise for reaching universal coverage. The association of favourable views of the CHiP cadre of staff with acceptance of interventions further suggests that the PopART model which uses CHiPs to deliver the HB-HTC intervention and facilitate linkage, is worth replicating in future implementation of UTT. We have also identified that self-perception of high risk sexual behaviour is facilitatory for uptake of interventions. Importantly, if individuals who engage in high risk sexual behaviour embrace interventions the prospect for treatment as prevention is optimistic.

7.6 References

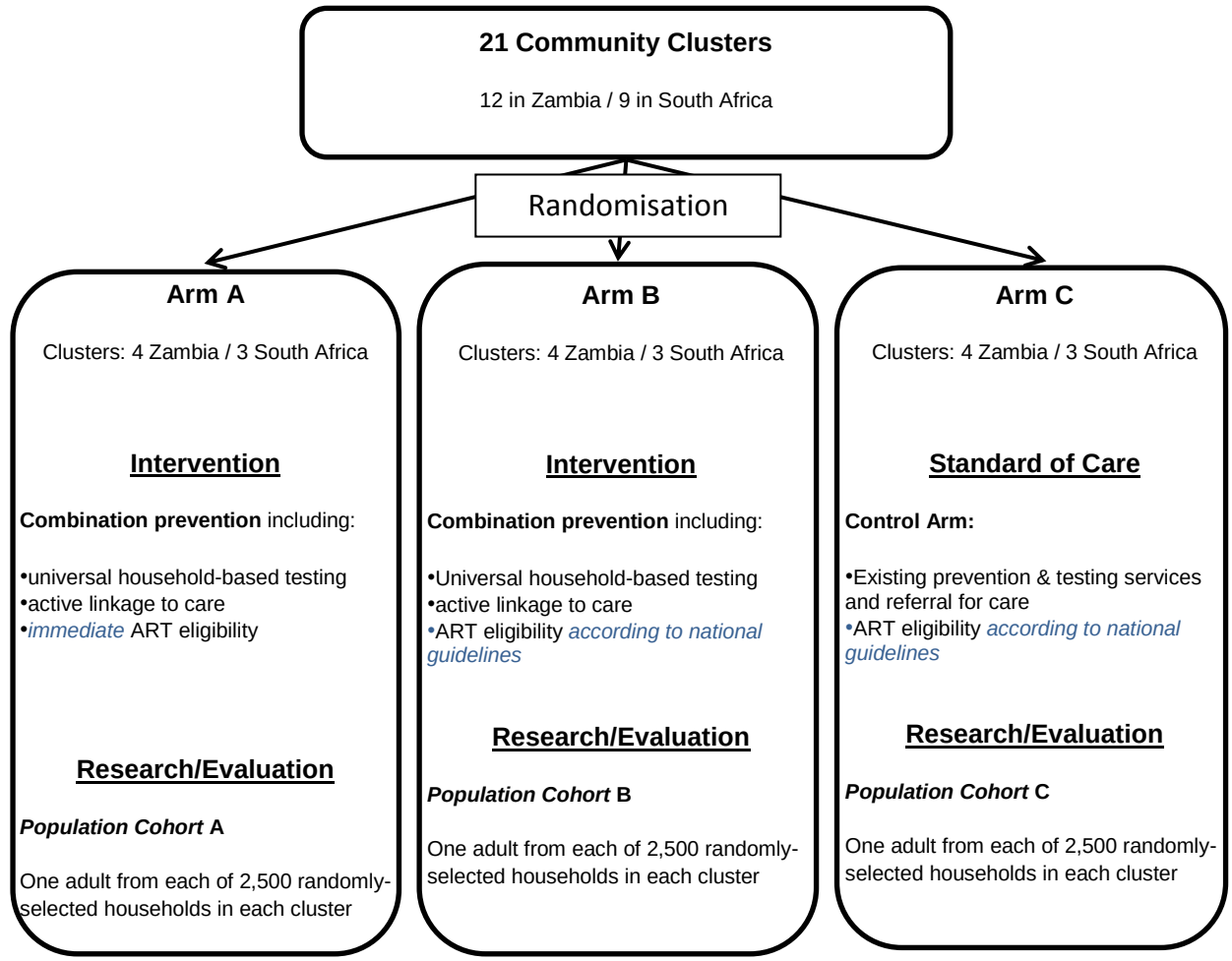
1. Iwuji CC, Orne-Gliemann J, Larmarange J, Okesola N, Tanser F, Thiebaut R, et al. Uptake of Home-Based HIV Testing, Linkage to Care, and Community Attitudes about ART in Rural KwaZulu-Natal, South Africa: Descriptive Results from the First Phase of the ANRS 12249 TasP Cluster-Randomised Trial. PLoS Med. 2016;13(8):e1002107.
2. Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med. 2013;10(8):e1001496.
3. Sharma M, Ying R, Tarr G, Barnabas R. Systematic review and meta-analysis of community and facility-based HIV testing to address linkage to care gaps in sub-Saharan Africa. Nature. 2015;528(7580):S77-85.
4. Hayes R, Floyd S, Schaap A, Shanaube K, Bock P, Sabapathy K, et al. A universal testing and treatment intervention to improve HIV control: One-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. PLoS Med. 2017;14(5):e1002292.
5. Iwuji C, Orne-Gliemann J, Balestre E, Larmarange J, Thiebaut R, Tanser F, et al. The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. http://programmeaids2016org/Abstract/Abstract/10537. 2016;Accessed on 19th Oct 2016.
6. Peterson M, Balzer L, Kwarsiima D, Sang D, Chamie G, Ayieko J, et al. SEARCH test and treat study in Uganda and Kenya exceeds the UNAIDS 90-90-90 cascade target by achieving 81% population-level viral suppression after 2 years. 21st International AIDS Conference, Durban. 2016;abstract WEAC0106LB.
7. Yang B, van Deventer D, Dunbar R, Bock P, Griffith S, Ayles H, et al. Working evening and weekend schedules is effective in reaching more men for home-based HIV testing: findings from HPTN 071 (PopART) in South Africa. 21st International AIDS Conference, Durban. 2016.
8. Naik R, Tabana H, Doherty T, Zembe W, Jackson D. Client characteristics and acceptability of a home-based HIV counselling and testing intervention in rural South Africa. BMC Public Health. 2012;12:824.
9. Barnabas R, van Rooyen H, Tumwisigye E, Brantley J, Baeten J, van Heerden A, et al. Uptake of antiretroviral therapy and male circumcision after community-based HIV testing and strategies for linkage to care versus standard clinic referral: a multisite, open-label, randomised controlled trial in South Africa and Uganda. Lancet HIV. 2016;Accessed on 10th March 2016.
10. Barnabas RV, van Rooyen H, Tumwesigye E, Murnane PM, Baeten JM, Humphries H, et al. Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: a prospective, observational intervention study. Lancet HIV. 2014;1(2):e68-e76.
11. van Rooyen H, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2013;64(1):e1-8.
12. Wynberg E, Cooke G, Shroufi A, Reid SD, Ford N. Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review. Journal of the International AIDS Society. 2014;17:18809.
13. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. AIDS. 2012;26(16):2059-67.
14. World Health Organization. Global report on urban health: equitable, healthier cities for sustainable development. http://wwwwhoint/kobe_centre/measuring/urban-global-report/ugr_full_reportpdf. 2016;Accessed on 22nd Nov 2016.
15. Boyer S, Iwuji C, Gosset A, Protopopescu C, Okesola N, Plazy M, et al. Factors associated with antiretroviral treatment initiation amongst HIV-positive individuals linked to care within a universal test and treat programme: early findings of the ANRS 12249 TasP trial in rural South Africa. AIDS care. 2016;28 Suppl 3:39-51.

16. Choko AT, MacPherson P, Webb EL, Willey BA, Feasy H, Sambakunsi R, et al. Uptake, Accuracy, Safety, and Linkage into Care over Two Years of Promoting Annual Self-Testing for HIV in Blantyre, Malawi: A Community-Based Prospective Study. PLoS Med. 2015;12(9):e1001873.
17. Mills EJ, Ford N. Home-based HIV counseling and testing as a gateway to earlier initiation of antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(2):282-4.
18. World Health Organization. Consolidated guidelines on HIV testing services. http://appswhoint/iris/bitstream/10665/179870/1/9789241508926_engpdf?ua=1&ua=1. 2015;Accessed on 26th July 2016.
19. Iwuji C, Orne-Gliemann J, Balestre E, Larmarange J, Thiebaut R, Tanser F, et al. The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. 21st International AIDS Conference, Durban. 2016;abstract FRAC0105LB.
20. Bemelmans M, Baert S, Goemaere E, Wilkinson L, Vandendyck M, van Cutsem G, et al. Community-supported models of care for people on HIV treatment in sub-Saharan Africa. Trop Med Int Health. 2014;19(8):968-77.

Appendices

Appendix 1 PopART Trial Schema

Source: PopART Trial Protocol Version 1.0(1)



Primary Outcome Measure

•HIV incidence measured over 3 years in ***Population Cohort***

Secondary Outcome Measures

•***Population Cohort***: HIV incidence measured over 1st , 2nd , and 3rd years, HSV-2 incidence, sexual risk behavior+, community VL*, viral suppression (ART patients)* , drug resistance (ART patients with detectable VL)*
•***Population Cohort*** and **Health Center Data:** ART Adherence, HIV disease progression and death, ART toxicity, HIV stigma
•**Health Center Data:** TB notification and mortality rates
•***Population Cohort*, Health Center Data, CHiPs Data:** uptake of PMTCT, uptake of male circumcision, ART screening and uptake, uptake of HIV testing and retesting, time between diagnosis and initiation of care

* Subject to funding for these assays.

1. HPTN 071 Protocol Team. HPTN 071 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa. http://wwwhptnorg/research_studies/hptn071asp. 2012.

Appendix 2: Information Sheet and Verbal Consent for Consideration of Case-control Study 1 (Zambia)

Information Sheet and Verbal Consent for Consideration of Case-control Study 1 (Zambia)

Factors associated with the uptake and non-uptake of Home-Based Voluntary HIV testing during the first annual round of the PopART * interventions - Case-control Study 1

*Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa

Introduction

This information sheet is about a study that is trying to identify why some people take-up home-based voluntary HIV testing offered by the PopART trial and why other people choose not to take-up this service. This study is called the case-control study 1 in PopART.

What is the purpose of the Case-control Study 1?

The case-control study 1 aims to understand the views and behaviours of community members who either accepted or did not accept the home-based voluntary HIV testing which was offered by CHiPs at peoples' homes. These questionnaires will let the researchers understand how the community feels about PopART trial activities.

What will happen during this study?

In each community, around 60 people will be asked whether they are willing to be interviewed by study researchers who will complete questionnaires based on answers participants give. You have been randomly selected – meaning you have not been singled out for any reason but the number on your CHiPs card was picked randomly from a list to be one of the people from your community who we would invite to participate in the study. If you participate in this study, you will undergo an interview with the researcher.

Where and who is conducting this study?

This study is being carried out in two countries, Zambia and South Africa, for a period of about1-2 months in 2014/2015. It will be done in 14 communities, 8 of which are in Zambia and 6 in South Africa. Researchers from the Zambia AIDS Related Tuberculosis Project and the Desmond Tutu TB Centre at Stellenbosch University, South Africa, and the London School of Hygiene and Tropical Medicine, UK will conduct the study. This study is being funded by the U.S. National Institutes of Health, the Office of the United States Global AIDS Coordinator, and the Bill and Melinda Gates Foundation.

What are you being asked?

At this point I am asking you for your permission to pass on your **name, address, date of birth and gender** to the researchers conducting the case-control Study 1 so that **they can approach you**. If you agree, the research team will be made aware that you **participated in the CHiPs programme**. **I will not pass on any other information about what you have told me as part of the CHiPs programme.** Then one of the researchers will come to find you and explain fully what the study involves. If you do

not agree now, I will not pass on any information, the research team will not approach you, and you will still receive all the services that are available to other community members here.

If you do agree for me to pass on your details to the research team, a researcher will explain the study to you. Once you fully understand what the study involves you will be asked for your written consent to participate in the study. At that time, you can decline to participate in the study if you decide not to proceed for any reason. If you decline, you will still receive all the services that are available to other community members here.

What are the possible risks or discomforts?

You may become embarrassed, worried or anxious when talking about your HIV status and discussing sexual risk behaviour and other topics. The researchers are trained to treat participants with respect, maintain confidentiality and to help you deal with any feelings or questions you have. You may feel that being part of this study could lead to you feeling stigmatized or separated from your community.

What are the potential benefits?

The benefit of agreeing to allow us to pass on your information to the research staff and for the research staff to come speak with you is the opportunity to participate in the study (if you agree). If you enrol in the study, you will be able express your opinions and represent views about yourself, your community and the PopART trial. This information will be anonymised and not be linked directly back to you. It will however help the research team understand how to improve HIV related services in the future. In addition, knowledge gained from this study may help reduce the spread of HIV in the future and promote better health for you and your family as well as helping with acknowledgement and acceptance of HIV as a community-wide health problem.

Persons to Contact for Problems or Questions

If you have any questions about this research study, your rights, or if you feel that you have experienced a research-related injury, contact:

Investigator of Record Name: *Dr Helen Ayles*

Research Site Address: *ZAMBART Project, School of Medicine, Ridgeway campus, Po Box 50697, Lusaka*

Daytime telephone number(s): *+260 211 254710*

If you have any questions or concerns about your rights or want to discuss a problem, get information or offer input, you may contact:

Independent Review Board/Ethics Committee: *UNZA Biomedical Research Ethics Committee*

Address of Independent Review Board: *School of Medicine, Ridgeway campus, Po Box 50110, Lusaka*

Daytime Telephone Number: *+260-211-256067*

Verbal Consent

Now I would like to find out if you have understood this information and if you agree to me passing on your **name, address, date of birth and gender** to the Case-Control Study 1 researchers along with

the fact that **you participated in the CHiPs programme**, so that **they can approach you** to explain and obtain full informed consent to participate in the study.

[*CHiP records in a log/electronic device the decision by the participant(s)*]

Appendix 3: Information Sheet and Informed Consent Case-control Study 1 (Zambia)

INFORMATION SHEET AND INFORMED CONSENT FORM FOR
CASE-CONTROL STUDY 1:

PARTICIPANT INFORMATION AND CONSENT FORM

Title of Research Study:	**Factors associated with the uptake and non-uptake of Home-Based Voluntary HIV testing during the first annual round of the PopART * interventions (Case-control Study 1) (*Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa)**
Protocol #:	HPTN 071, Version 1.0, 26 October 2012 DAIDS ID: 11865
Sponsor:	National Institute of Allergy and Infectious Diseases National Institute of Mental Health (U.S. National Institutes of Health) Office of the United States Global AIDS Coordinator Bill and Melinda Gates Foundation
Investigator of Record:	Professor Nulda Beyers
Research Site Address (es):	

Site: Delft South Clinic **Address:** Cr Main Rd & Boyce St	**Site:** Bloekombos Clinic **Address:** Sam Nokasela Avenue	**Site:** Ikwhezi clinic **Address:** Simon Street Nomzame
Site: Town 2 Clinic (outreach) **Address:** c/o Zibonele and Manyano Street	**Site:** Kuyasa Clinic **Address:** Ntlazana Street, Khayelitsha	**Site:** Luvuyo Clinic **Address:** Hlela Road, Makaza
Site: Dalevale Clinic (outreach) **Address:** Symphony Avenue,	**Site:** Cloetesville Clinic **Address:** Tennant Street	**Site:** Wellington Clinic (outreach) **Address:** Wellington Municipality

Daytime telephone number(s):	**021 983 9114**
24-hour contact number(s):	**083 572 1470**

Participant Information and Consent Form

Please ask the study investigator or the study staff to explain any words or procedures that you do not clearly understand.

The PopART trial is looking at ways to reduce HIV incidence in your community. Information about the trial is supplied in the document which you may already have received from the Community HIV-care Providers (CHiPs) who have been visiting households in this community (Provide CHiPs Information sheet (see separate document) if needed – document which would have already been provided to all community members at the time of providing the intervention). The purpose of this form is to give you information about a research study you are being asked to join. The study is trying to identify why some people take-up home-based voluntary HIV testing offered by the PopART trial and why other people choose not to take-up this service. If you sign this form, you will be giving your permission to take part in the study. The form describes the purpose, procedures, benefits, and risks of the research study. You should take part in the study only if you want to do so. You may choose not to join the research project or withdraw from this study at any time. Choosing not to take part in this research will not in any way affect the health care or benefits that you or your family will receive. Please read this t Information and Consent Form and ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

This study is being funded by the U.S. National Institutes of Health, the Office of the United States Global AIDS Coordinator, and the Bill and Melinda Gates Foundation

Your participation is voluntary

You do not have to take part in this study. If you decide today to take part in this research project, you may refuse to take part in any portion of the study or stop at any time without reducing or affecting any care that you receive at the health centers in your community.

Purpose of the PopART Research in the Communities

The HPTN 071 or PopART trial is testing a program to try to reduce HIV infection in a community like yours. Twenty one communities that include about 600,000 adults are included in this research (about 400,000 adults in twelve Zambian communities and 200,000 adults in nine South African communities, all located in the Western Cape).

In some communities, the level of care that people are used to will stay the same, in terms of HIV testing, and care of those who have HIV.

In other communities, to make HIV testing easier, CHiPs will go to all homes and will offer to do an HIV test on those wishing to have a test. (In South Africa children over the age of twelve can choose to have an HIV test without getting permission from their parents or guardians although it is better to first get consent from parents or guardians). For anyone infected with HIV, they will be offered to start taking drugs to treat HIV according to the standard treatment guidelines that are in place in the Western Cape. The health workers will visit every home again once a year for up to three more years to repeat the HIV testing and to refer people to care.

In other communities, CHiPs will go to all houses offering HIV testing, as was just described. In these communities if someone over the age of 18 tests HIV positive however, they will be offered to start taking medicines to treat HIV right away. The CHiPs will visit every home again once a year for up to three more years to repeat the HIV testing and to refer people to care. Children under the age of 18 who test HIV positive will be offered care according to the standard treatment guidelines used in the Western Cape.

At the end of the trial, the researchers will see if offering HIV tests in each household and offering people the chance to start HIV treatment right away has reduced the number of people with HIV infection in the community. They will also see if starting ART early has any negative effects on people's health.

Your community is one of the communities participating in this research. If health care workers are visiting homes in your community, you will notice that they provide some other information and services to people, but the most important thing is the testing and HIV treatment they offer.

What is the purpose of the Case-control study?

In each community, around 60 people will be asked to participate in additional activities such as completing questionnaires. These questionnaires will let the researchers understand how the community feels about the program. You have been selected to be one of the 60 people from your community who we are asking to participate in these additional activities to represent the views and behaviours of community members who either accepted or did not accept the home-based voluntary HIV testing which was offered by the PopART CHiP workers at peoples' homes. That is why you are being asked to read this document.

What will happen during this study?

If you participate in this study, you will undergo an interview with the researcher who has presented this information to you. We will ask you questions about a number of topics including you and your sexual practices, HIV testing, male circumcision, and how you and others feel about HIV.

The PopART CHiPs keep records of all their clients. We would like to look at your records to help us better understand how the study activities in the community are being taken up over time and how they are affecting the health of people diagnosed with HIV. In addition, and for the same reasons, we would like to access the routine patient records kept at the health center for HIV-infected patients. If you agree to participate in this study, we will ask you for your permission to look at your records from the household and, if applicable, at the health center.

What are the possible risks or discomforts?
You may become embarrassed, worried or anxious when talking about your HIV status and discussing sexual risk behavior and other topics. A trained staff member will help you deal with any feelings or questions you have. You may feel that being part of this study could lead to you feeling stigmatized or separated from our community

What are the potential benefits?
During the study, you will be able express your opinions and represent views about yourself, your community and the PopART trial. This information will be coded and not be linked directly back to you. It will however help us understand how to improve HIV related services in the future. In addition, knowledge gained from this study may help reduce the spread of HIV in the future and promote better health for you and your family as well as helping with acknowledgement and acceptance of HIV as a community-wide health problem.

Our research staff will provide you with advice on any services that may be of help to you, if we identify problems that you are experiencing.

Are there any alternatives to participation?
If you decide not to participate in this study, you will still receive all the services that are available to other community members here.

How will my confidentiality and privacy be protected?
We cannot guarantee absolute confidentiality. However, we will do everything possible to protect your confidentiality if you join this study. We do this by giving you a study number and any information will be labeled with this number only, so only the research staff will be able to link this number to your name. Your personal information (name, address, phone number) will be protected by the research staff. This information will not be used in any publication of information about this study.

To protect your privacy, you will meet with the researcher in a private area where others cannot overhear conversations with you.

People who may review your records include: [insert name of site IRB/EC], local regulatory agencies, US National Institutes of Health (NIH), study staff, and study monitors. Institutional Review Boards

(IRBs) or Ethics Committees (ECs) are committees that watch over the safety and rights of research participants.

What happens if I am injured by participating in this study?
It is very unlikely that you could be injured as a result of participating in this study. However, if you are injured while participating in this study, you will be given immediate treatment for your injuries. You will not] have to pay for this care. Stellenbosch University does have is a/ insurance cover for serious research related injury compensation. You will not be giving up any of your legal rights by signing this Participant Information and Consent Form.

What are some reasons why I may be withdrawn from this activity without my consent?
You may be withdrawn from the study without your consent for the following reasons:

- The research study, or this part of the study, is stopped or canceled
- The study staff feels that completing the study or this part of the study would be harmful to you or others

The study will be conducted according to the international Declaration of Helsinki and other applicable international ethical codes for research on human participants.

This study has been approved by a research ethics committee from Stellenbosch University

Persons to Contact for Problems or Questions
If you have any questions about your participation in this research study, your rights as a research subject, or if you feel that you have experienced a research-related injury, contact:

- Dr Peter Bock, Co-Investigator, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch. Telephone: 021 9389062. Email: peterb@sun.ac.za

- Principal Investigator: Nulda Beyers, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch. Telephone: 021 938 9114. Email:nb@sun.ac.za

- Mr Franklin Weber, HREC coordinator, Health Research Committee 1, Stellenbosch University Health Research Ethics Committee, Tygerberg Campus. Telephone: 021 938 9657.

PARTICPANTS STATEMENT OF CONSENT

Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa

- I have been given sufficient time to consider whether to take part in this study.
- My taking part in this research study is voluntary. I may decide not to take part or to withdraw from the research study at any time without penalty or loss of benefits or treatment to which I am entitled.
- The research study may be stopped at any time without my consent.
- I have had an opportunity to ask my study investigator questions about this research study. My questions so far have been answered to my satisfaction.
- I have been told how long I may be in the research study.
- I have been informed of the procedures that may be performed during the research study.
- I have been told what the possible risks and benefits are from taking part in this research study. I may not benefit if I take part in this research study.
- I do not give up my legal rights by signing this form.
- I have been told that before any study related procedures being performed, I will be asked to voluntarily sign this Participant Information and Consent Form.
- I will receive a signed and dated copy of this Information and Consent Form.

If you have either read or have heard the information in this Participant Information and Consent Form, if all of your questions have been answered, and if you agree to take part in the study, please print and sign your name and write the date on the line below.

Access of Data from PopART Community Health Worker Records

_____ My initials indicate that I agree to allow my data from the PopART Community Health Worker Records to be accessed and used for this study.

_____ I do not agree to allow my data from the PopART Community Health Worker Records to be accessed and used for this study.

Access of Data from Heath Center

_____ My initials indicate that I agree to allow my records at the health center to be accessed and used for this study.

_____ I do not agree to allow my health care records to be accessed and used for this study.

I voluntarily agree to take part in this research study.

---------- ----------

Subject's Name (print) **Subject's Signature and Date**

I certify that the information provided was given in a language that was understandable to the subject.

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Name of Study Staff Conducting Consent Discussion (print) **Study Staff Signature and Date**

---------- ----------

Witness' Name (print) (As appropriate) Date **Witness' Signature and Date**

Appendix 4: CC1 questionnaire

Case- Control Study 1 Questionnaire

	Item / Question	Display Response Options	Skip Pattern	Rationale for Q	Comments (for phrasing of Qs or issues for training of RAs)
Attempt_1	Record the results of your attempt to locate the randomly-selected household member for interview. Attempt 1: [dd][mm][yy], Has the participant been met?; Attempt 2; [dd][mm][yy] Has the participant been met?; Attempt 3; [dd][mm][yy]Has the participant been met?; … "add more"	1. Yes- Individual participant is available; 2. No, participant is not available. I will make further attempts to contact; 3. No, this is my final attempt to contact the participant.	If 1, go to "Language"; if 3 , go to "Attempt 2"		
Attempt_2	Record the outcome of the final attempt to reach the participant.	1. Individual absent (expected to return to community); 2.Individual moved out from community; 3.Individual deceased; 4.Individual incapacitated/in hospital; 5.Individual incarcerated; 6. Other	End of survey, go to "home screen"		

Lang	Select appropriate language for the participant survey	**Zambia:** English only; English + Bemba; English + Nyanja; English + Lozi; English + Tonga. **South Africa:** English only; English + Afrikaans; English + Xhosa; None	If "none" end of survey, go to Ineligible_0		
Agree_1	Thank you for taking the time to speak with me about a study on services provided by the PopART trial. I have been given your name and address by a PopART CHiP who has said you agreed to talk him/her about what services PopART was offering and also that you agreed that I could come to talk to you about another study. Please note, they did not pass on any other information about what you told them or any medical information about you. Can I proceed?	Yes; No	If yes, go to "Details"; if no continue	Note 1, this refers to the fact that CHiP had previosuly asked permission and ppt agreed - ie not cold-calling. Note 2: For ppts who still don't remember who CHiP are, PopART leaflet will be provided to refresh ppt's memory. Note 3: The RA will be kept blind to ppt test uptake (and Case v Control) status - up until the end of this study (see HIV_test section) to minimise interviewer bias.	

Agree_2	What was the main reason the participant did not agree?	Time constraints; Confidentiality concerns; Spouse did not agree; Changed his/her mind; Does not want to (unspecified reason);No response; Other	Go to "Declined Study Participation" (Dec_01)		
Agree_3	Can I come back at another time that might be more suitable?	Yes; No	If no go to "Declined Study Participation" (Dec_01)		
Agree_4	Record when to return	Time and date field			Must be within 2 week window
Details	I need to check some details before deciding whether it is suitable for us to continue with the study. Can I proceed?				
Inclusion_DoB	What is your date of birth?	Date; Don't know			
Inclusion_Age	What is your age?	XX	If <18y (but shouldn't be as pre-checked from CHiPs EDC before random selection as potential ppt), continue but ineligible so Skip to Ineligible_0 before Consent Qs		
Dem_Gen	(Record ppt's gender)	Male; Female			

Dem_Disab_1	Do you have any disabilities? (RA to choose all that apply from):	No, No Disability; Sight (blind/severe visual impairment; Hearing (deaf/profoundly hard of hearing); Communication (speech impairment); Physical (needs wheelchair/ crutches/stick); Mental disability; Other	Mark all that apply. If "no, no disability" continue; if yes go to Excl_HIV_res		
Excl_Disab	Does the disability prevent participation in the study?	Yes; No	If yes, continue but ineligible so Skip to Ineligible_0 before Consent Qs		RA judgement - this Q will put some people into Ineligible therefore is an exclusion Q. RA training to only exclude eg if ppt is non-verbal/ no mental capacity. Criteria will be defined and provided at RA training.
Excl_HIV research	Are you currently involved in any other HIV research study ?"	Yes; No		RA to probe and verify eg not referring to PopART intervention itself	Note, not an exclusion but want to record it.

Excl_PC	Are you currently involved in the Population Cohort of the PopART study?	Yes; No	If yes, continue but ineligible so Skip to Ineligible_0 before Consent Qs		RA to probe and ascertain (ie not intervention but PC). Participation in other CC is also Excl criterion but we would exclude this overlap at the time of selection of potential candidates from EDC register.
Excl_staff	Are you or any member of your HH working as staff on the PopART trial?	Yes; No	If yes go to ineligibility text; if no continue.		
Consent_1	I would like to take some time to explain the research that we are carrying out in this study - a study about services provided by the PopART trial. At the end of that you can decide whether you would like to participate and continue with answering specific questions for the study. Before we begin, do you have any questions?				
Consent_2	Obtain consent (as per language on consent form)				
Consent_3	Did the individual give consent to participate in the study ?	Yes; No	If yes, continue; if no go to "Consent _6"		

Consent_4	Is the participant literate?	Yes; No	If yes, go to Consent_7	Only to determine if witness is required (eligible to participate either way).	Use literacy tool
Consent_5	Who acted as a witness?	1.Family member;2 Neighbour;3 Health care ;4. Other	Go to Consent_7		ie this Q only for those illiterate
Consent_6	What was the main reason the participant did not consent?	Time constraints; Confidentiality concerns; Spouse did not agree; No witness available/refused witness; Did not want to (unspecified reason); Other	Go to "Declined Study Participation" (Dec_01)		Pilot reasons
Consent_7	Did the participant give consent to access further records from CHiPs EDC and routine health centre records?	Yes; No		Ppt can decline this part and still be in CC study.	Only if consented to CC study.
Ineligible_0	Thank you very much for your cooperation. The information you provided is very helpful and we appreciate your time and assistance. Unfortunately, you do not meet our specific eligibility criteria for this particular study. This does not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Thank you again for your willingness to participate in this study. Do you have any final questions or comments that you would like to share with me?		go to End_01		

Declined_0	Thank you for your time. Your decision not to participate in this particular study does not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Do you have any final questions or comments that you would like to share with me?		go to End_01		
Intro	Thank you for agreeing to take part in this study. I would like to ask you a few questions. Your answers in this study are completely confidential. This means that they will not be shared with anyone outside of the study team (including the CHiPs) in a way that can be connected to you. No one will know what particular answers you give. The answers you give do not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Some of these questions may be uncomfortable for you. Please remember that you don't have to answer any questions that you don't want to and we can stop the interview at any time. If I ask about something that makes you feel uncomfortable,				

	just let me know and we can consider skipping the question. Our discussion will last just over an hour.				
Dem_Edu	What is the highest grade of education that you have completed? Please choose one from:	None; Grade 1; Grade 2; Grade 3; Grade 4; Grade 5; Grade 6; Grade 7; Grade 8; Grade 9; Grade 10; Grade 11; Grade 12; College/University; other			
Dem_Nation	What is your nationality?	list of all African countries; other	If not South Africa or Zambia, go to "Dem_relig_1"		

Dem_Ethnic	What is your ethnic group? Please choose one from:	**If Zambia**- drop down Bemba, Tonga , Chewa, Lozi, Nsenga, Tumbuka, Ngoni, Lala, Kaonde, Lunda, Luvale, Lenje, Ila, Bisa, Ushi, Chishinga, Ng'umbo, Lamba, Mbunda, Lungu, Mambwe, Namwanga, Seng, other **If SA** – drop down Xhosa, Zulu, Venda, Sotho, Tsonga, Tswana, Fengu, Afrikaner, Cape Coloured, Indian South Africans, Pakistani South Africans, other			
Dem_Relig_1	What is your religion? Please choose one from:	Christian; Islam; Baha'i faith; Buddhism; Hinduism; Judaism; Animist; Traditionalist; No religion ; Other	If not Christian, go to "Dem_Marr"	This Q is being asked as it has relevance wrt to uptake of our services / competing services offered by faith healers etc. Also, we may see a particular group associated with non-uptake which might indicate need for better engagement with that group's religous leaders etc.	

Dem_Relig_2	What is your denomination? Please choose one from:	Roman Catholic ; Anglican ; Seventh-Day Adventist; Baptist; Pentecostal; Salvation Army; Lutheran; Evangelical church; United Methodist/African Methodist; Jehovah's witness; New Apostolic church (NAC); Apostolic faith Mission (AFM); Zion Christian Church (ZCC)Other		As above.	
Dem_Marr_1	Are you currently married or living as married?	Yes; No	If yes, go to "Dem_Child_1"		Yes if any of Traditional/legal/western according to country norms - training issue
Dem_Marr_2	Have you ever been married? Please choose one from:	never married; divorced/separated; widowed; No Answer			
Dem_Child_1	To how many children are you a parent or guardian?	# (includes 0)			All alive.Includes step-children; nieces/nephews which ppt cares for (self-defined)
Dem_Work_1	Are you currently working?	Yes; No	If no, go to "Dem_Work_3"		

Dem_Work_2	In your main job what type of work do you do? Please choose one from:	Occasional employment; Seasonal employment; Casual employment; Formal wage employment, full-time; Formal wage employment, part time; Self-employed in agriculture; Self-employed making money, full-time; Self-employed making money, part-time; Other	Go to "Dem_Work_4"		
Dem_Work_3	What is the reason why you are not working? Please choose one from:	Waiting to continue agricultural work; Unemployed (looking for work);Unemployed (waiting to start new work);Unable to work (permanently sick or injured);Student; Housewife/homemaker (not looking for work);Other, not looking for work			
Dem_Work_4	Describe the work that you do or did in your most recent job. If you have more than one profession, choose the one you spend the most time doing. Please choose one from:	Farmer (own land);Farm work on employers land; Domestic ;Work in bar, hotel, guest house; Fishing; Mining; Working in shop; Informal Selling; Commercial sex work; Transport (trucker, taxi driver);Factory ; Guard (security company);Police/soldier; Clerical and office work; Government ; Teacher; health care ; Other Professional; Other			

Dem_Comm	How long have you lived in this community?	XX in years, months, weeks or days			Best guess/estimate
Dem_Abs_1	In the last 3 months, how many nights did you spend away from home?	# nights	If 0, go to HH_1		RA training - "night spent" away = slept away
Dem_Abs_2	In the last 3 months, how many nights did you spend outside this community [community name]?	# nights	If 0, go to HH_1		as above
Dem_Abs_3	What was the main reason you spent time outside this community - on the last occasion when you were away? Please choose one from:	work or business; visiting family/leisure/holiday; other			only if ppt was away in last 3 months ie ≥1 for Q above; train RA to ask ppt to pick most appropriate (eg ppt may have work and visit family - pick main one based on greatest time spent).
Dem_Abs_4	How often do you usually spend time away from this community for the above reason? Please choose one from:	>once ever 3 months; once every 3 months; once every 6 months; once every year; once every >1year			once = one episode (not one night/day)
Dem_Abs_5	In the last year, how many nights did you spend outside this community [community name]?	# nights			Include last 3 months + other nights away in last year (less complicated)
Dem_Abs_6	What was the main reason you spent time outside this community over the last year? Please choose one from:	work or business; visiting family/leisure/holiday; other			

Dem_Abs_7	How often do you usually spend time away from this community for the above reason?	>once ever 3 months; once every 3 months; once every 6 months; once every year; once every >1year			
HH_1	Total Household Members	#			Including ppt
HH_2	Are you the Head of HH?	Yes; No	If yes go to Econ_Hous_1		
HH_3	How are you related to the Head of HH. Is he/she your ...? Please choose one from:	Husband; father; father-in-law; brother, brother-in-law; son, son-in-law; grandfather; uncle; nephew; Wife; mother; mother-in-law; sister; sister-in-law; daughter; daughter-in-law; grandmother; aunt; niece; cousin; friend; landlord; other			
Econ_Hous_1	Which of the following best describes the main type of building that this household occupies? Please choose one from:	single unit/brick structure on its own stand; cluster/multi-unit; traditional hut/structure made from traditional material; flat in block of flats; servant quarters; caravan/tent; hostel; shack; other			
Econ_Hous_2	What is the main type of flooring for this household? Please choose one from:	Dirt/earth; Wood/plank; Parquet; Lino; Cement; Tile; Other			
Econ_Hous_3	How many living and sleeping rooms are there in this housing unit? Please choose one from:	XX rooms			

Econ_Hous_4	What is the main source of drinking water for this household? Please choose one from:	Piped indoors; Stand pipe/tap within plot; communal tap; borehole; Protected well; Unprotected/shallow well river/dam/lake/pan; bowser/tanker; other			
Econ_Hous_5	What is the main source of energy used for cooking? Please choose one from:	No cooking done in household; Electricity (mains);Electricity (individual solar); Gas; Paraffin; Charcoal; Wood; Other			
Econ_Hous_6	What is the main toilet facility used in your household? Please choose one from:	Own flush toilet; Shared flush toilet; own pit latrine; Shared pit latrine; Own VIP latrine; Shared VIP latrine; Pail/bucket; Communal chemical latrine; Bush; Other			
Econ_Ass	Does any member of your household have access to the following items in good working order? Please choose all that apply from:	Working Cellphone; bicycle; motorcycle or scooter; car/bakkie; Electricity to house; TV; Fridge/freezer; Radio; Computer/Laptop; CD or MP3 player; stereo/cassette /other music player;			Select all that apply
Econ_Inc_2	Do you or anyone in your household receive any government grants?	Yes; No			

Econ_Contr	Do you make decisions about how money is spent in your household? Please choose one from:	Yes (someone else's approval needed); Yes (no one else's approval needed); No		There is evidence that suggests women who have some financial autonomy, are more likely to take-up and follow-up with PMCT care, so I am interested in exploring similar for test uptake	
CHiP_exp_0	I would now like to ask you some Qs about your experience with the CHiP who came to your house to offer you services related to PopART. The information you give us will help the PopART team learn what they are doing well and what could be done better. Your answers in this study are completely confidential, will not be shared with CHiPs and the answers you give do not affect any of the services available to you (including the services provided by the CHiPs). Also, I don't know whether you had a test with the PopART CHiP and it makes no difference to these next questions.Do you have any questions before we begin?				Note, in trainings it will be highlighted that it is important that RA is seen as separate from CHiPs. One is research the other intervention

CHiP_exp_1	This question is regarding the CHiP(s) who came to see you. Did you previously know the individual(s) BEFORE you first met them as a CHiP?	Yes; No			(If more than 1 CHiP - any of them); rely on ppts own definition of "know" someone
CHiP_exp_2	Did you know which community they come from when you first met them as a CHiP?	Yes; No	If yes, continue, if no go to CHiP_exp_4		
CHiP_exp_3	Do they come from this community (XX community name)?				
CHiP_exp_4	Please choose one from the following about whether you think confidentiality will be maintained after your encounter(s) with the ChiP?	Strongly agree; Agree; Disagree; Strongly Disagree			Training point - confidentiality still maintained if result discussed with ppt's permission/ for pt management. But breach of confidentiality if any client details discussed with other community members etc.
CHiP_exp_5	Please choose one from the following about whether you think that in general, the CHiP treated you with respect?	Strongly agree; Agree; Disagree; Strongly Disagree			
CHiP_exp_6	Please choose one from the following about whether you think that in general, the CHiP was someone you could talk to and answer questions openly?	Strongly agree; Agree; Disagree; Strongly Disagree			

CHiP test_peer_0	For the next 4 Qs, please think about the first time when you met the CHiP and they offered you an HIV test.			Note the CC study will be done upto 9m after the first encounter. We are trying to get at how the ppt felt at the time of deciding whether to take up testing. From CHiP EDC we will know time-line of when offer was first made and if multiple offers were made before test was accepted among controls. Recall bias is a valid concern but we will try our best!	Ensure these next Qs are related to first encounter as CHiP (eg for those who knew the CHiP worker previously)
CHiP test_peer_1	At that first time when you met the CHiP and they offered you an HIV test, did you already know beforehand, people who had accepted HIV testing by CHiPs?	Yes; No	If no go to CHiP test_peer_3	Focus on testing of a peer by CHiP as the key peer influence on the ppt's own uptake of CHiP HBT ie not looking at other test uptake.	RA training - "already know" should not incluide those who are being offered testing at the same time as ppt
CHiP test_peer_2	Who was it you knew, who had accepted HIV testing by the CHiP? Please choose <u>all</u> that apply:	Sexual partner; Household member(s) (not including sexual partner); friend(s)/neighbour(s)/colleague(s); other			RA training to avoid double-counting (sexual partner and HH member)

CHiP test_peer_3	How many other HH members (not including yourself) were present you were first offered HIV testing by CHiPs?	XX	If 0, go to Sex_0		
CHiP test_peer_4	How many HH members (not including yourself) accepted testing when offered HIV testing by CHiPs at that time?	XX			
CHiP test_peer_5	Was your partner present when you were offered testing at home by the CHiPs?	Yes; No			
Sex_0	Now I would like to ask you some questions about your recent sexual activity. I know these questions are sensitive and want to remind you that your answers are completely confidential. Scientists are interested to know about patterns of sexual behaviours in the community and this information will not be linked to you as an individual. If anyone comes near us I will change the topic of conversation. If we should come to any questions that you don't want to answer, just let me know and we can decide if we should skip the question. Do you have any questions before we continue?				
Sex_1	Have you ever had sex (meaning penetrative intercourse)?	Yes; No			

Sex_2	How old were you when you had sex for the first time? If you can't recall the exact age, please give a best guess.	XX years			
Sex_3	In your lifetime how many different people have you had sex with (including your husband/wife)? If you can't recall the exact number, please give a best guess.	XXX sexual partners			
Sex_4	Have you had sex in the past 12 months?	Yes; No	If No go to Stigma_0		
Sex_00	At this point, let me say that I understand that some of the Qs I ask you may seem inappropriate for your situation. Please know that I am asking them as part of standard list of questions which I have to ask everyone and I appreciate your patience and honesty when answering them, remembering that your answers will be kept confidential.				
Sex_5	In the past 12 months, how many different people have you had sex with (including your husband/wife)? If you can't recall the exact number, please give a best guess.	XXX people		If 1 partner go to Part_one_0; 2 partners go to Part_two_0; ≥ 3 go to Part_three_0 (if 0 partners this Q would be skipped see - Sex_4 skip pattern)	
Sex_6	..., do any live outside of [community name]?	Yes; No; Don't now			

Part_one_0	I would like to ask more questions about the partner with whom you have had sex most recently. In order to ask the questions we will call this partner - Partner 1. Can I proceed?		Go to Part_one_1		
Part_two_0	I would like to ask more questions about the 2 partners with whom you have had sex most recently. In order to ask the questions we will list these 2 partners by number and then I will ask the same set of questions about each partner in turn. We will start with the partner you have had sex with most recently - who we will refer to as Partner 1. Can I proceed?		Go to Part_one_1 (which will be followed by same loop questions for Part_two)		
Part_three_0	I would like to ask more questions about the 3 partners with whom you have had sex most recently. In order to ask the questions we will list these 3 partners by number and then I will ask the same set of questions about each partner in turn. We will start with the partner you have had sex with most recently - who we will refer to as Partner 1. Can I proceed?		Go to Part_one_1 (which will be followed by same loop questions for Part_two; then Part_three)		

Part_one_1	What was your relationship with "this partner 1" the last time you had sex? Please choose one from:	Husband/wife (i.e. married or living as married); Boyfriend/ Girlfriend; Casual partner known to you before having sex; One-time partner who was unknown to you before having sex; Other			
Part_one_2	Where was "this partner 1" living the last time you had sex?	Same house; Same community [insert name of this community]; Outside [insert name of this community]; Don't Know			
Part_one_3	How old is "this partner 1" ? If you don't know for sure, please give a best guess.	XX years			
Part_one_4	When did you first have sex with "this partner 1"? (Best guess)	MM/YYYY			
Part_one_5	How long ago did you last have sex with "this partner 1" ? If you are not sure, please give a best guess.	xxx days; Use calendar and help work out number of days.			
Part_one_6	The last time you had sex with "this partner 1" , did you/your partner use a condom?	Yes; No; Don't remember	If Yes, continue; If Don't remember or No answer go to Part_one_11		Can be male or female condom
Part_one_7	Did you drink alcohol before the last time you had sex with "this partner 1" ?	Yes; No; Don't remember			
Part_one_8	The last time you had sex with "this partner 1" , did you give or were you given money or a gift in order to have sex? It could be money (eg rent or fees for something), food, soap, transport, or clothing.	Yes, I Received money/gift; Yes, I gave money/gift; No, I did not give or receive money/gift	If yes, skip to Part_one_14 OR if Part_one_1 response is husband/wife, skip to Part_one_14		

Part_one_9	What is the HIV status of "this partner 1" ?	Positive; Negative; Don't know	If Negative or Don't know, go to Part1_16		
Part_one_10	Do you know if "this partner 1" is taking ART?	Yes, he/she is taking; No, he/she is not taking; Don't know			
Part_one_11	Over the past 12 months, during your relationship with "this partner 1" , do you know or suspect that this partner was having sex with someone else?	Yes – I know with another spouse; Yes – I know with another partner or partners; Yes - I believe there was another partner or partners; No, I know this partner did not have other partners; Don't know			
			If Sex_5=2 or Sex_5=3, proceed with partner loop Qs for each partner (max 3)		Programme loop Qs to repeat according to answer in Sex_5
HIV self_risk_1		Very high; somewhat high; somewhat low; very low			Training - to ensure prompting that if partner perceived to be high risk, this will be a "yes" for the ppt too (even if eg ppt is monogamous)
Stigma_0	I am going to ask you about issues relevant to HIV and taking an HIV test. Using your own opinions and thinking about this community [community name], please tell me how strongly you agree or disagree to the following				

	statements. Do you have any questions before we begin?				
Stigma_1	I fear that I could contract HIV if I come into contact with the saliva of a person living with HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_2	I would be ashamed if someone in my family had an HIV test	Strongly agree; Agree; Disagree; Strongly Disagree			Training point - Q is about taking a test ie not about HIV +ve result
Stigma_3	People are hesitant to take an HIV test due to fear of other people's reaction if the test result is positive for HIV.	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_4	People sometimes talk badly about people who have had or who are thought to have had an HIV test.	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_5	I would not buy fresh vegetables from a vendor if I knew that this person had had an HIV test	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_6	People may think that I have been immoral/irresponsible as the reason behind having an HIV test	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_7	People receive verbal abuse or insults because of having an HIV test	Strongly agree; Agree; Disagree; Strongly Disagree			

Stigma_8	People fear other people's reaction if the test result is positive for HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_9	People are ashamed if the test result is positive for HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Health_0	I will now ask you questions about whether you have been unwell in the last 12? months. Do you have any questions before we begin?				
Health_1	During the past 12 months have you been unwell to the extent that you needed to seek advice about it?	Yes; No			
Health_2	If yes, approximately how many times in the last 12 months?	# (if not sure, best guess)			
Health_3	During the past 12 months which of the following did you go to for health care/treatment - please choose all that apply from:	Traditional/faith healer; Health worker at a health facility; Pharmacy or other drug vendor; other			All that apply
Health_4	In general, which of these would you consult first for a health related problem (if anyone)? Please choose one from:	Traditional/faith healer; Health worker at a health facility; Pharmacy or other drug vendor			Only one
Health_5	During the past 12 months, have you had to stay overnight in hospital for any illnesses?	Yes; No	If no, go to Health_8		
Health_6	During the past 12 months, how many times have you been hospitalised?	# times			
Health_7	During the past 12 months, what was the total duration of hospitalisation?	# days			

Health_8	During the past 12 months, have you paid for private health care?	Yes; No			Private health - may include HIV testing/ treatment/admission.
Circum_0	Now I would like to ask you about male circumcision. As a reminder, by male circumcision, I mean removal of the foreskin of the penis. I understand these Qs can be sensitive. The reason that I am about to ask them is so scientists can understand circumcision practices in this community, because medical male circumcision has been shown to be associated with HIV transmission. I would be grateful if you could answer as honestly as possible remembering that your answers are confidential. Before we begin, do you have any questions?		Only if Dem_Gen:Male		
Circum_1	Are you circumcised?	Yes; No; not sure;	If No, not sure, No answer go to SRQ_0		
Circum_2	At what age were you circumcised?	< 5years of age; XX years			
Circum_3	When were you circumcised?	MM/YYYY		This is to identify if MC was after PopART start	If VMMC done - use circumcision "certificate" or other proof if available; if not - ppt self-report

Circum_4	What was the main reason why you were circumcised?	Tradition or religious; To protect myself against HIV; Hygiene; Other medical reason; Other; Don't know	If Don't know or No answer go to Circum_06		
Preg_0	I will now ask you questions about pregnancy and antenatal care. Do you have any questions before we begin?		Only if Dem_Gen:Female		
Preg_1	How many times have you given birth? Include both live births and stillbirths. Multiple births, such as twins, count as 1 birth.	# times	If #:0 go to SRQ_0		
Preg_2	When was the last birth?	MM/YYYY	If last birth < 12m ago continue, if >12m go to SRQ_0		
Preg_3	Did you go for antenatal care during this pregnancy?	Yes; No			
Preg_4	Were you tested for HIV during this pregnancy?	Yes; No; Don't know	If yes go to Preg_5; If no, go to Preg_6; If Don't know go to SRQ_0		
Preg_5	When was that?	MM:YYYY (if not sure, best guess)	Go to Preg_7		
Preg_6	Why were you not tested for HIV during this pregnancy?	Did not agree to testing; Not offered / did not attend a clinic where testing is available; Husband/partner refused; Already knew I was HIV positive; other	Go to SRQ_0+D148		
Preg_7	If you feel comfortable, were you given ART for you to take to protect your baby?	Yes;No; Don't know; Not yet received; Already on ART before attending ANC			

SRQ_0	The following questions are related to certain pains and problems, that may have bothered you in the last 30days. If you think the question applies to you and you had the problem described in the last 30days, answer YES. On the other hand, if the question does not apply to you and you did not have the problem in the last 30days, answer NO.If you are unsure please give the best answer you can. To remind you again, all your reponses are confidential.				Yes =1 and score of 6 or greater = suggestive of mental disorder
SRQ_1	Do you often have headaches?	Yes; No			
SRQ_2	Is your apetite poor?	Yes; No			Poor apetite = low interest in food
SRQ_3	Do you sleep badly?	Yes; No			
SRQ_4	Do you cry more than usual?	Yes; No			
SRQ_5	Do you find it difficult to enjoy your daily activities?	Yes; No			
SRQ_6	Do you find it difficult to make decisions?	Yes; No			
SRQ_7	Is your daily work suffering?	Yes; No			
SRQ_8	Are you unable to play a useful part in life?	Yes; No			
SRQ_9	Has the thought of ending your life been on your mind?	Yes; No			
SRQ_10	Do you feel tired all the time?	Yes; No			- for reasons that cannot be explained

Alcohol_0	I will now ask you questions about drinking alcohol and drug use. I know these questions are sensitive and want to remind you that your answers are completely confidential. Do you have any questions before we begin?				
Alcohol_1	How often do you have a drink containing alcohol?	(0) Never ; (1) Monthly or less; (2) 2 to 4 times a month; (3) 2 to 3 times a week; (4) 4 or more times a week REVERSE ORDER OF OPTIONS	If zero go to Alc_9		Training - reassure ppts that Alc_9 and 10 are std and still asked of everyone even if score here is zero.
Alcohol_2	How many drinks containing alcohol do you have on a typical day when you are drinking?	(0) 1 or 2; (1) 3 or 4; (2) 5 or 6; (3) 7, 8, or 9; (4) 10 or more			
Alcohol_3	How often do you have six or more drinks on one occasion?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily	Skip to Alc_9 if Total Score for Questions 2 and 3 = 0		
Alcohol_4	How often during the last 12 months have you found that you were not able to stop drinking once you had started?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_5	How often during the last 12 months have you failed to do what was normally expected from you because of drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_6	How often during the last 12 months have you needed a first drink in the morning to get yourself going after a heavy drinking session?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			

Alcohol_7	How often during the last 12 months have you had a feeling of guilt or remorse after drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_8	How often during the last 12 months have you been unable to remember what happened the night before because you had been drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_9	Have you or someone else been injured as a result of your drinking?	(0) No ; (2) Yes, but not in the last year; (4) Yes, during the last year			
Alcohol_10	Has a relative or friend or a doctor or another health been concerned about your drinking or suggested you cut down?	(0) No ; (2) Yes, but not in the last year; (4) Yes, during the last year			
Alcohol_11	Among people of similar age and sex as you in this community during an average month, how common do you think it is for them to have six or more drinks on one occasion?	Very common; somewhat common; somewhat uncommon; very uncommon			
Drugs_1	In your lifetime have you ever used any drugs recreationally?	Yes; No	If no or refused – If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		
Drugs_2	In the last 12 months, have you used drugs recreationally?	Yes; No	If no or refused – If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		

Drugs_3	In the last 12 months, which drugs have you used?	Cannabis/Marijuana; Cocaine/Crack; Khat/Miraa; Ecstasy/Disco biscuit; Heroin; Amphetamine/Speed;Tik; Nyamba (any drug mixed with ART and smoked); Glue/solvents/petrol sniffing;Other	If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		
IPV_0	I would now like to ask you some questions about your relationship(s) and how any partner during the last 12 months treated you. If anyone comes near us I will change the topic of conversation. I would again like to assure you that your answers will be kept confidential. If we should come to any questions that you don't want to answer, just let me know and we can decide if we need to skip the question. Do you have any questions before I begin?			There could be different ways of addressing the issue of GBV - but on balance we have gone with any partner of last 12m and Qs related specifically to IPV ie not overall violence women may be subjected to in the community (so does not include rape by a stranger etc).I think this is the most pertinent to explore wrt asso with uptake of testing. Qs are largely based on DHS questions.	

IPV_1	In the last 12 months, how often has a partner verbally insulted you or humiliated you in front of other people, or intimidated or threatened to hurt you?	Often; A few times; Once; Never	If no go to IPV_3		Training to emphasise this Q is about non-physical/sexual abuse rather verbal/ other intimidation.
IPV_2	When was the last time any of the above happened?	MM:YYYY			Approximate
IPV_3	In the last 12 months, how often has a partner physically hurt you eg slapped, kicked, pushed, punched, beaten or otherwise physically hurt you?	Often; A few times; Once; Never	If no go to IPV_5		
IPV_4	When was the last time any of the above happened?	MM:YYYY			Approximate
IPV_5	In the last 12 months, how often has a partner made you have sexual activities when you did not want to?	Often; A few times; Once; Never	If no go to IPV_7		Check best language to use - would prefer to avoid too strong a word as women will be less inclined to say yes (eg avoiding "rape" or "forced"). Other thoughts?
IPV_6	When were you last made to have sexual activities when you did not want to?	MM:YYYY			Approximate
IPV_7	In this community how common do you think it is for people to believe a husband is justified in physically hurting his wife if he has a reason?	Very common; somewhat common; somewhat uncommon; very uncommon			

IPV_8	In this community how common do you think it is for people to believe a husband is justified in making his wife have sexual activities with him if he wants to?	Very common; somewhat common; somewhat uncommon; very uncommon			
IPV_!!	If experience of IPV - I'm sorry to hear about what has happened to you. If you wish we can provide information on what help might be available for you, before I leave.				Programme prompt at end of survey to provide further information.
Percep_0	I am going to provide you with some statements about HIv testing and about the PopART trial and would like you to choose the most appropriate response. As before, your answers will not be shared with anyone outside of the study team (including the CHiPs) in a way that can be connected to you. The answers you give do not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Can I proceed?				

Percep_1	The activities promoted by the PopART trial can increase the number of people having an HIV test in your community	Strongly agree; Agree; Disagree; Strongly Disagree		If ppts unclear about the activities - RAs can illustrate using study inforamtion sheets which ppts are routinely given by CHiPs in PopART intervention communities	
Percep_2	The activities promoted by the PopART trial can increase the number of people having treatment for HIV in your community	Strongly agree; Agree; Disagree; Strongly Disagree			
Percep_3	Maximising the number of HIV infected individuals on treatment can help reduce the amount of new HIV infections arising in your community	Strongly agree; Agree; Disagree; Strongly Disagree			
Percep_4	Condoms are not required to prevent HIV transmission if infected individuals are on treatment	Strongly agree; Agree; Disagree; Strongly Disagree			
Percep_5	What do you think about the PopART trial being delivered in your community	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it	If Strongly agree or Agree, go to Percep_7		
Percep_6	Which of these is the most important explanation for why you disagree with the PopART trial being delivered in your community? Please choose all that apply from:	The CHiPs workers ask too many questions; the CHiPs workers pressure people to test for HIV or to talk to them; HIV testing/talking about HIV at home is not a good idea; doing research in my community is not a good idea; other			

Percep_7	What do you think about talking to household members together in a group about HIV testing (including offering HIV testing) at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			Training - this is about group pre-test cuoneling and offer of testing (not necessarily including testing itself)
Percep_8	What do you think about talking to couples together about HIV testing (including offering HIV testing) at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			
Percep_9	What do you think about providing household members results of HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it		ie full disclosure	
Percep_10	What do you think about providing couples results of HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it		ie full disclosure	
PrevT_1	Have you ever been tested for HIV?	Yes; No	If No, go to FavCHT_0		
PrevT_2	How many times have you had an HIV test? If you do not remember the number of times, give a best guess.	# of times			
PrevT_3	The last time you were tested for HIV, where were you tested?	Government hospital or clinic (includes ANC, TB, etc.); Private/church/mission hospital or clinic; Stand-alone HIV testing centre; Mobile testing site(caravan, tent, etc.; Work place; Home with CHiP; Home not with CHiP; Other place			

PrevT_4	When was the last time you were tested for HIV? If you don't know the exact date, give a best guess.	MM:YYYY			
PrevT_5	Have your disclosed the result of you last HIV test with anyone? (not including me)	Yes; No			
	Different factors may influence someone's choice on whether to take up HIV testing. The following sets of questions are about the factors which may have encouraged or discouraged you from testing with the CHiP. Consider these questions about pros and cons for you regardless of your final decision ie whether you tested with the CHiP or not.				RA training Q is about pros/cons around HIV testing when offered by CHiP not just any HIV testing
FavCHT_0	When offered a test by the PopART CHiP, did any of the following encourage you towards having an HIV test?				
FavCHT_1	I have never had an HIV test and wanted to learn my status	Yes; No			
FavCHT_2	I recently tested HIV negative and wanted to re-check	Yes; No			
FavCHT_3	I just believed I was HIV negative and wanted to check	Yes; No			
FavCHT_4	I knew a current/previous sexual partner was/is HIV positive so I wanted to know my status	Yes; No			
FavCHT_5	I suspected (not confirmed) I had an HIV positive partner so I wanted to know my status	Yes; No			

FavCHT_6	I was sick and suspected it was because of HIV	Yes; No			
FavCHT_7	HIV is very common in this community so I thought I might be positive	Yes; No			
FavCHT_8	I thought my current/past sexual behaviour put me at high risk of getting HIV	Yes; No			
FavCHT_9	Many people I know had tested with a CHiP so I wanted to as well	Yes; No			
FavCHT_10	I wanted to be able to get treatment without delay if I tested and was HIV-positive	Yes; No			
FavCHT_11	I accepted the advice of the CHiP that it was a good idea to test	Yes; No			
FavCHT_12	I accepted as I had no special reason to decline	Yes; No			
FavCHT_13	Would there be some other reason we have not already taked about?	Yes; No			
AgCHT_0	When offered a test by the PopART CHiP, did any of the following discourage you from having an HIV test?				
AgCHT_1	I had difficulty with the time it would take - because of my livelihood/job	Yes; No			
AgCHT_2	I had difficulty with the time it would take - because of housework	Yes; No			
AgCHT_3	I was worried that someone I did not want to know, would find out that I was having an HIV test	Yes; No	If no, go to AgCHT_5		

AgCHT_4	Who was it that you did not want knowing that you were having an HIV test? Please choose all that apply:	Sexual partner; Household member(s) (not including sexual partner); friend(s)/neighbour(s)/colleague(s); other			
AgCHT_5	I was worried that someone I did not want to know, would find out if I tested HIV-positive	Yes; No	If no, go to AgCHT_7		
AgCHT_6	Who was it that you did not want knowing that you were having an HIV test? Please choose all that apply:	Sexual partner; Household member(s) (not including sexual partner); friend(s)/neighbour(s)/colleague(s); other			
AgCHT_7	I did not want to find out my HIV status because I was afraid of a positive test result	Yes; No			
AgCHT_8	I was confident I was HIV-negative and didn't need to test	Yes; No			
AgCHT_9	I believed I was HIV-positive and didn't need to test to find out	Yes; No			
AgCHT_10	I already had a test recently and did not want to test again	Yes; No			
AgCHT_11	I was not comfortable having an HIV test at home	Yes; No			
AgCHT_12	I didn't want to have an HIV test done by the particular CHiP who offered it to me	Yes; No			
AgCHT_13	I don't think I am at risk of HIV	Yes; No			
AgCHT_14	I am not ready to find out my HIV status	Yes; No			
AgCHT_15	I just did not want to find out my HIV status (no particular reason)	Yes; No			

AgCHT_16	Was there some other reason we have not already covered?	Yes; No			
CHT_1	Did you accept the test when offered by the PopART CHiP ?	Yes; No	If yes, go to CHT_3	Note this is saved until the end to minimise interviewer bias as to whether a ppt is a case or control	
CHT_2	In your own words why did you decide not to test with a PopART CHiP?		Go to Result_1		RA to select most suitable from drop-down menu - same list as AgCHT
CHT_3	In your own words what was your main reason for testing with a PopART CHiP?				RA to select most suitable from drop-down menu - same list as FavCHT
Result_1	If you feel comfortable, would you mind telling me what the result of your last HIV test was?	HIV-negative; HIV-positive; Not comfortable/Don't know	Skip Q if PrevT_1=No		Note, for Cases (declined CHiP test) this will relate to any other HIV test; Programme to skip this Q if earlier response was - never had a test before.

Further research participation permission	If you are interested, we would like to enter your name on a list from which you may be selected to participate in further research. Would you be interested in being included in such a list? If so, we will enter your name, address, date of birth and gender on a list and a researcher will come to explain the next study to you. Once you fully understand what the study involves you will be asked for your written consent to participate in the study. At that time, you can decline to participate in the study if you decide not to proceed for any reason. If you decline at any stage, you will still receive all the services that are available to other community members here. Would you be interested in being included in such a list?	Yes;No			
Concl_0	Thank you very much for your cooperation. The information you provided is very helpful and we appreciate your time and assistance. Do you have any final questions or comments that you would like to share with me?		Go to End_01		
IPV	For participants with experience of IPV - provide contact information of police				

	and NGOs working on IPV support				

Appendix 5: Information Sheet and Verbal Consent for Consideration of Case-control Study 2 (South Africa)

Consideration for Case-control Study 2 -

Information Sheet and Verbal Consent by CHiPs (South Africa)

Introduction

This information sheet is about a study that is trying to identify why some people start antiretroviral treatment (ART) without delay after being referred by the PopART Community HIV-care Providers (CHiPs) and why other people choose not to or delay starting treatment. This study is called the Case-Control Study 2 in PopART.

What is the purpose of the Case-Control study 2?

The Case-control study 2 aims to understand the views and behaviours of community members who started ART without delay, after being referred by the PopART CHiPs compared with those who delayed starting treatment, or not at all. These questionnaires will let the researchers understand how the community feels about the treatment being offered in PopART Arm A communities which your community …… *(community name),* is a part of.

What will happen during this study?

In each community, approximately 120 people will be asked whether they are willing to be interviewed by study researchers who will complete questionnaires based on answers participants give. You have been randomly selected – meaning you have not been singled out for any reason but the number on your CHiPs card was picked randomly from a list to be one of the people from your community who we would invite to participate in the study. If you participate in this study, you will undergo an interview with the researcher.

Where and who is conducting this study?

This study is being carried out in two countries, Zambia and South Africa, for a period of about 5 years from 2012 to 2017. It will be done in 21 communities, 12 of which are in Zambia and 9 in South Africa. Researchers from the Zambia AIDS Related Tuberculosis Project and the Desmond Tutu TB Centre at Stellenbosch University, South Africa, will work closely together with colleagues from different institutions including the Ministry of Health (Zambia) and the Department of Health (South Africa). This study is being funded by the U.S. National Institutes of Health, the Office of the United States Global AIDS Coordinator, and the Bill and Melinda Gates Foundation.

What are you being asked to do?

At this point I am asking you for your permission to pass on your **name, address, date of birth and gender** to the researchers conducting the Case-control Study 2 so that **they can approach you**. The research team will be made aware that you **were referred for HIV care at the clinic by the CHiPs**. **I will not pass on any other information about what you have told me as part of the CHiPs programme.** If you agree, one of the researchers will come to find you at home and explain fully what the study involves. If you do not agree now, I will not pass on any information and you will still receive all the services that are available to other community members here.

If you do agree for me to pass on your details to the research team, a researcher will come to explain the study to you. Once you fully understand what the study involves you will be asked for your written consent to participate in the study. At that time, you can decline to participate in the study if you decide not to proceed for any reason. If you decline, you will still receive all the services that are available to other community members here.

What are the possible risks or discomforts?

You may become embarrassed, worried or anxious when talking about your HIV status and discussing sexual risk behavior and other topics. The researchers are trained to treat participants with respect, maintain confidentiality and to help you deal with any feelings or questions you have. You may feel that being part of this study could lead to you feeling stigmatized or separated from your community.

What are the potential benefits?

During the study, you will be able express your opinions and represent views about yourself, your community and the PopART trial. When producing results your information will be anonymised and not be linked directly back to you. The results will however help the research team understand how to improve HIV related services in the future. In addition, knowledge gained from this study may help reduce the spread of HIV in the future and promote better health for you and your family as well as helping with acknowledgement and acceptance of HIV as a community-wide health problem.

Persons to Contact for Problems or Questions

If you have any questions about this research study, your rights, or if you feel that you have experienced a research-related injury, contact:

Investigator of Record Name: *Professor Nulda Beyers and Dr Peter Bock*

Research Site Address: *Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch*

Daytime telephone number(s): *+27 21 983 9114 and +27 21 938 9062*

Health Research Committee: *Health Research Committee 1, Stellenbosch University Health Research Ethics Committee, Tygerberg Campus, Stellenbosch University*

Daytime Telephone Number: *+27 21 938 9657*

Verbal Consent

Now I would like to find out if you have understood this information and if you agree to me passing on your **name, address, date of birth and gender** to the Case-Control Study 2 researchers along with the fact that **were referred for HIV care at the clinic by the CHiPs** so that **they can approach you** to explain and obtain full informed consent to participate in the study.

[*CHiP records in a log the decision by the participant(s)*]

Appendix 6: Information Sheet and Informed Consent Case-control Study 2 (South Africa)

INFORMATION SHEET AND INFORMED CONSENT FORM FOR
CASE-CONTROL STUDY 2:

PARTICIPANT INFORMATION AND CONSENT FORM

Title of Research Study:	**Factors associated with the uptake and non-uptake of immediate antiretroviral treatment during the first annual round of the PopART * interventions (*Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa)**
Protocol #:	HPTN 071, Version 1.0, 26 October 2012 DAIDS ID: 11865
Sponsor:	National Institute of Allergy and Infectious Diseases National Institute of Mental Health (U.S. National Institutes of Health) Office of the United States Global AIDS Coordinator Bill and Melinda Gates Foundation
Investigator of Record:	Professor Nulda Beyers
Research Site Address (es):	

Site: Delft South Clinic **Address:** Cr Main Rd & Boyce St	**Site:** Bloekombos Clinic **Address:** Sam Nokasela Avenue	**Site:** Ikwhezi clinic **Address:** Simon Street Nomzame
Site: Town 2 Clinic (outreach) **Address:** c/o Zibonele and Manyano Street	**Site:** Kuyasa Clinic **Address:** Ntlazana Street, Khayelitsha	**Site:** Luvuyo Clinic **Address:** Hlela Road, Makaza
Site: Dalevale Clinic (outreach) **Address:** Symphony Avenue,	**Site:** Cloetesville Clinic **Address:** Tennant Street	**Site:** Wellington Clinic (outreach) **Address:** Wellington Municipality

Daytime telephone number(s):	**021 983 9114**
24-hour contact number(s):	**083 572 1470**

Participant Information and Consent Form

Please ask the study investigator or the study staff to explain any words or procedures that you do not clearly understand.

The PopART trial is looking at ways to reduce HIV incidence in your community. Information about the trial is supplied in the document which you may already have received from the Community HIV-care Providers who have been visiting households in this community (Provide CHiPs Information sheet – see separate document). The purpose of this form is to give you information about a research study you are being asked to join. The study is trying to identify why some people start antiretroviral treatment soon after being recommended it by PopART community health workers and why other people choose not to start or delay starting treatment. If you sign this form, you will be giving your permission to take part in the study. The form describes the purpose, procedures, benefits, and risks of the research study. You should take part in the study only if you want to do so. You may choose not to join the research project or withdraw from this study at any time. Choosing not to take part in this research will not in any way affect the health care or benefits that you or your family will receive. Please read this t Information and Consent Form and ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

This study is being funded by the U.S. National Institutes of Health, the Office of the United States Global AIDS Coordinator, and the Bill and Melinda Gates Foundation

Your participation is voluntary

You do not have to take part in this study. If you decide today to take part in this research project, you may refuse to take part in any portion of the study or stop at any time without reducing or affecting any care that you receive at the health centers in your community.

Purpose of the PopART Research in the Communities

The HPTN 071 or PopART trial is testing a program to try to reduce HIV infection in a community like yours. Twenty one communities that include about 600,000 adults are included in this research (about 400,000 adults in twelve Zambian communities and 200,000 adults in nine South African communities, all located in the Western Cape).

In some communities, the level of care that people are used to will stay the same, in terms of HIV testing, and care of those who have HIV.

In other communities, to make HIV testing easier, community health care workers will go to all homes and will offer to do an HIV test on those wishing to have a test. (In South Africa children over the age of twelve can choose to have an HIV test without getting permission from their parents or guardians although it is better to first get consent from parents or guardians). For anyone infected with HIV, they will be offered to start taking drugs to treat HIV according to the standard treatment guidelines that are in place in the Western Cape. The health workers will visit every home again once a year for up to three more years to repeat the HIV testing and to refer people to care.

In other communities, health care workers will go to all houses offering HIV testing, as was just described. In these communities if someone over the age of 18 tests HIV positive however, they will be offered to start taking medicines to treat HIV right away. The health workers will visit every home again once a year for up to three more years to repeat the HIV testing and to refer people to care. Children under the age of 18 who test HIV positive will be offered care according to the standard treatment guidelines used in the Western Cape.

At the end of the trial, the researchers will see if offering HIV tests in each household and offering people the chance to start HIV treatment right away has reduced the number of people with HIV infection in the community. They will also see if starting ART early has any negative effects on people's health.

Your community is one of the communities participating in this research. If health care workers are visiting homes in your community, you will notice that they provide some other information and services to people, but the most important thing is the testing and HIV treatment they offer.

What is the purpose of the Case-Control study?

In each community, around 120 people will be asked to participate in additional activities such as completing questionnaires. These questionnaires will let the researchers understand how the community feels about the program. You have been selected to be one of the people from your community who we are asking to participate in these additional activities to represent the views and behaviours of community members who either did or did not initiate antiretroviral treatment within 3 months of being recommended it by PopART community health workers. That is why you are being asked to read this document.

What will happen during this study?

If you participate in this study, you will undergo an interview with the researcher who has presented this information to you. We will ask you questions about a number of topics including you and your sexual practices, HIV testing, male circumcision, and how you and others feel about HIV.

The PopART community health care workers and staff at the health center keep records of all their clients and patients as part of their normal procedures. We would like to look at these records collected at the household, and medical records for any study participant who is HIV infected. Doing so will help us better understand how the study activities in the community are being taken up over time and how they are affecting the health of people diagnosed with HIV. If you agree to participate in this study, we will ask you for your permission to look at your records from the household and at the health center.

What are the possible risks or discomforts?
You may become embarrassed, worried or anxious when talking about your HIV status and discussing sexual risk behavior and other topics. A trained staff member will help you deal with any feelings or questions you have. You may feel that being part of this study could lead to you feeling stigmatized or separated from our community

What are the potential benefits?
During the study, you will be able express your opinions and represent views about yourself, your community and the PopART trial. This information will be coded and not be linked directly back to you. It will however, help us understand how to improve HIV related services in the future. In addition, knowledge gained from this study may help reduce the spread of HIV in the future and promote better health for you and your family as well as helping with acknowledgement and acceptance of HIV as a community-wide health problem.

Our research staff will provide you with advice on any services that may be of help to you, if we identify problems that you are experiencing.

Are there any alternatives to participation?
If you decide not to participate in this study, we will refer you to other places where you can receive an HIV test. If it is offered in your community, you can also receive testing from a health worker visiting your home during the study period.

How will my confidentiality and privacy be protected?
We cannot guarantee absolute confidentiality. However, we will do everything possible to protect your confidentiality if you join this study. We do this by giving you a study number and any information will be labeled with this number only, so only the research staff will be able to link this number to your name. Your personal information (name, address, phone number) will be protected by the research staff. This information will not be used in any publication of information about this study.

To protect your privacy, you will meet with the researcher in a private area where others cannot overhear conversations with you.

People who may review your records include: [insert name of site IRB/EC], local regulatory agencies, US National Institutes of Health (NIH), study staff, and study monitors. Institutional Review Boards (IRBs) or Ethics Committees (ECs) are committees that watch over the safety and rights of research participants.

What happens if I am injured by participating in this study?
It is very unlikely that you could be injured as a result of participating in this study. However, if you are injured while participating in this study, you will be given immediate treatment for your injuries. You will not] have to pay for this care. Stellenbosch University does have is a/ insurance cover for serious research related injury compensation. You will not be giving up any of your legal rights by signing this Participant Information and Consent Form.

What are some reasons why I may be withdrawn from this activity without my consent?
You may be withdrawn from the study without your consent for the following reasons:

- The research study, or this part of the study, is stopped or canceled
- The study staff feels that completing the study or this part of the study would be harmful to you or others

The study will be conducted according to the international Declaration of Helsinki and other applicable international ethical codes for research on human participants.

This study has been approved by a research ethics committee from Stellenbosch University

Persons to Contact for Problems or Questions
If you have any questions about your participation in this research study, your rights as a research subject, or if you feel that you have experienced a research-related injury, contact:

- Dr Peter Bock, Co-Investigator, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch. Telephone: 021 9389062. Email: peterb@sun.ac.za

- Principal Investigator: Nulda Beyers, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch. Telephone: 021 938 9114. Email:nb@sun.ac.za

- Mr Franklin Weber, HREC coordinator, Health Research Committee 1, Stellenbosch University Health Research Ethics Committee, Tygerberg Campus. Telephone: 021 938 9657.

PARTICPANTS STATEMENT OF CONSENT

Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa

- I have been given sufficient time to consider whether to take part in this study.
- My taking part in this research study is voluntary. I may decide not to take part or to withdraw from the research study at any time without penalty or loss of benefits or treatment to which I am entitled.
- The research study may be stopped at any time without my consent.
- I have had an opportunity to ask my study investigator questions about this research study. My questions so far have been answered to my satisfaction.
- I have been told how long I may be in the research study.
- I have been informed of the procedures that may be performed during the research study.
- I have been told what the possible risks and benefits are from taking part in this research study. I may not benefit if I take part in this research study.
- I do not give up my legal rights by signing this form.
- I have been told that before any study related procedures being performed, I will be asked to voluntarily sign this Participant Information and Consent Form.
- I will receive a signed and dated copy of this Information and Consent Form.

If you have either read or have heard the information in this Participant Information and Consent Form, if all of your questions have been answered, and if you agree to take part in the study, please print and sign your name and write the date on the line below.

Access of Data from PopART Community Health Worker Records

_____ My initials indicate that I agree to allow my data from the PopART Community Health Worker Records to be accessed and used for this study.

_____ I do not agree to allow my data from the PopART Community Health Worker Records to be accessed and used for this study.

Access of Data from Heath Center

_____ My initials indicate that I agree to allow my records at the health center to be accessed and used for this study.

_____ I do not agree to allow my health care records to be accessed and used for this study.

I voluntarily agree to take part in this research study.

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Subject's Name (print) **Subject's Signature and Date**

I certify that the information provided was given in a language that was understandable to the subject.

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Name of Study Staff Conducting Consent Discussion (print) **Study Staff Signature and Date**

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Witness' Name (print) (As appropriate) Date **Witness' Signature and Date**

Appendix 7: CC2 questionnaire

	Item / Question	Display Response Options	Skip Pattern	Rationale for Q	Comments (for phrasing of Qs or issues for training of RAs)
Attempt_1	Record the results of your attempt to locate the randomly-selected household member for interview. Attempt 1: [dd][mm][yy], Has the participant been met?; Attempt 2; [dd][mm][yy] Has the participant been met?; Attempt 3; [dd][mm][yy]Has the participant been met?; … "add more"	1. Yes- Individual participant is available; 2. No, participant is not available. I will make further attempts to contact; 3. No, this is my final attempt to contact the participant.	If 1, go to "Language"; if 3 , go to "Attempt 2"		
Attempt_2	Record the outcome of the final attempt to reach the participant.	1. Individual absent (expected to return to community); 2.Individual moved out from community; 3.Individual deceased; 4.Individual incapacitated/in hospital; 5.Individual incarcerated; 6. Other	End of survey, go to "home screen"		
Lang	Select appropriate language for the participant survey	**Zambia:** English only; English + Bemba; English + Nyanja; English + Lozi; English + Tonga. **South Africa:** English only; English + Afrikaans; English + Xhosa; None	If "none" end of survey, go to Ineligible_0		

Agree_1	Thank you for taking the time to speak with me about a study on services provided by the PopART trial. I have been given your name and address by a PopART CHiP who has said you agreed to talk him/her about what services PopART was offering and that you were referred to the clinic for HIV care. I was also informed that you agreed that I could come to talk to you about another study. Please note, they did not pass on any other information about what you told them or any medical information about you. Can I proceed?	Yes; No	If yes, go to "Details"; if no continue	Note 1: this refers to the fact that CHiP had previosuly asked permission and ppt agreed - ie not cold-calling. Note 2: For ppts who still don't remember who CHiP are, PopART leaflet will be provided to refresh ppt's memory. Note 3: the RA will be kept blind to ppt treatment status (and Case v Control status) - up until as late into the survey as possible to minimise interviewer bias.	
Agree_2	What was the main reason the participant did not agree?	Time constraints; Confidentiality concerns; Spouse did not agree; Changed his/her mind; Does not want to (unspecified reason);No response; Other	Go to "Declined Study Participation" (Dec_01)		
Agree_3	Can I come back at another time that might be more suitable?	Yes; No	If no go to "Declined Study Participation" (Dec_01)		

Agree_4	Record when to return	Time and date field			Must be within 2 week window
Details	I need to check some details before deciding that you meet the criteria for the study.				
Inclusion_DoB	What is your date of birth?	Date; Don't know			
Inclusion_Age	What is your age?	XX	If <18y (but shouldn't be as pre-checked from CHiPs EDC before random selection as potential ppt), continue but ineligible so Skip to Ineligible_0 before Consent Qs		
Dem_Gen	(Record ppt's gender)	Male; Female			
Dem_Disab_1	Do you have any disabilities?	No, No Disability; Sight (blind/severe visual impairment; Hearing (deaf/profoundly hard of hearing); Communication (speech impairment); Physical (needs wheelchair/ crutches/stick); Mental disability; Other	Mark all that apply. If "no, no disability" continue; if yes go to Excl_HIV_res		

Excl_Disab_1	Does the disability prevent participation in the study?	Yes; No	If yes, continue but ineligible so Skip to Ineligible_0 before Consent Qs		RA judgement - this Q will put some people into Ineligible therefore is an exclusion Q. RA training to only exclude eg if ppt is non-verbal/ no mental capacity. Criteria will be defined and provided at RA training.
Excl_HIV research	Are you currently involved in any other HIV research study?"	Yes; No		RA to probe and verify eg not referring to PopART intervention itself	Note, not an exclusion but want to record it.
Excl_PC	Are you currently involved in the Population Cohort of the PopART study ?"	Yes; No	If yes, continue but ineligible so Skip to Ineligible_0 before Consent Qs		RA to probe and ascertain (ie not intervention but PC). Participation in other CC is also Excl criterion but we would exclude this overlap at the time of selection of potential candidates from EDC register
Excl_staff	Are you or any member of your HH working as staff on the PopART trial?	Yes; No	If yes go to Ineligible_0; if no continue.		

Consent_1	I would like to take some time to explain the research that we are carrying out in this study - a study about services provided by the PopART trial. At the end of that you can decide whether you would like to participate and continue with answering specific questions for the study. Before we begin, do you have any questions?				
Consent_2	Obtain consent (as per language on consent form)				
Consent_3	Did the individual give consent to participate in the study ?	Yes; No	If yes, continue; if no go to "Consent _6"		
Consent_4	Is the participant literate?	Yes; No	If yes, go to Consent_7		Use literacy tool
Consent_5	Who acted as a witness?	1.Family member;2 Neighbour;3 Health care ;4. Other	Go to Consent_7		ie this Q only for those illiterate
Consent_6	What was the main reason the participant did not consent?	Time constraints; Confidentiality concerns; Spouse did not agree; No witness available/refused witness; Did not want to (unspecified reason); Other	Go to "Declined Study Participation" (Dec_01)		Pilot reasons
Consent_7	Did the participant give consent to access further records from CHiPs EDC and routine health centre records?	Yes; No		Ppt can decline this part and still be in the main CC study if consented above (see wording in IC form).	Only if consented to CC study.

Ineligible_0	Thank you very much for your cooperation. The information you provided is very helpful and we appreciate your time and assistance. Unfortunately, you do not meet our specific eligibility criteria for this particular study. This does not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Thank you again for your willingness to participate in this study. Do you have any final questions or comments that you would like to share with me?		go to End_01		
Declined_0	Thank you for your time. Your decision not to participate does not affect any of the services available to you in this community or elsewhere. Do you have any final questions or comments that you would like to share with me?		go to End_01		

Intro	Thank you for agreeing to take part in this study. I would like to ask you a few questions. Your answers in this study are completely confidential. This means that they will not be shared with anyone outside of the study team (including the CHiPs) in a way that can be connected to you. No one will know what particular answers you give. The answers you give do not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise. Some of these questions may be uncomfortable for you. Please remember that you don't have to answer any questions that you don't want to and we can stop the interview at any time. If I ask about something that makes you feel uncomfortable, just let me know and we can consider skipping the question. Our discussion will last just over an hour.				
Dem_Edu	What is the highest grade of education that you have completed? Please choose one from:	None; Grade 1; Grade 2; Grade 3; Grade 4; Grade 5; Grade 6; Grade 7; Grade 8; Grade 9; Grade 10; Grade 11; Grade 12; College/University; other			

Dem_Nation	What is your nationality?	list of all African countries; other	If not South Africa or Zambia, go to "Dem_relig_1"		
Dem_Ethnic	What is your ethnic group? Please choose one from:	**If Zambia**- drop down Bemba, Tonga , Chewa, Lozi, Nsenga, Tumbuka, Ngoni, Lala, Kaonde, Lunda, Luvale, Lenje, Ila, Bisa, Ushi, Chishinga, Ng'umbo, Lamba, Mbunda, Lungu, Mambwe, Namwanga, Seng, other **If SA** – drop down Xhosa, Zulu, Venda, Sotho, Tsonga, Tswana, Fengu, Afrikaner, Cape Coloured, Indian South Africans, Pakistani South Africans, other			
Dem_Relig_1	What is your religion? Please choose one from:	Christian; Islam; Baha'i faith; Buddhism; Hinduism; Judaism; Animist; Traditionalist; No religion ; Other	If not Christian, go to "Dem_Marr"	This Q is being asked as it has relevance wrt to uptake of our services / competing services offered by faith healers etc. Also, we may see a particular group associated with non-uptake which might indicate need for better	

				engagement with that group's religous leaders etc.	
Dem_Relig_2	What is your denomination? Please choose one from:	Roman Catholic ; Anglican ; Seventh-Day Adventist; Baptist; Pentecostal; Salvation Army; Lutheran; Evangelical church; United Methodist/African Methodist; Jehovah's witness; New Apostolic church (NAC); Apostolic faith Mission (AFM); Zion Christian Church (ZCC)Other			
Dem_Marr_1	Are you currently married or living as married?	Yes; No	If yes, go to "Dem_Child_1"		Yes if any of Traditional/legal/western according to country norms - training issue
Dem_Marr_2	Have you ever been married? Please choose one from:	never married; divorced/separated; widowed; No Answer			
Dem_Child_1	To how many children are you a parent or guardian?	# (includes 0)			

Dem_Work_1	Are you currently working?	Yes; No	If no, go to "Dem_Work_3"		
Dem_Work_2	In your main job what type of work do you do? Please choose one from:	Occasional employment; Seasonal employment; Casual employment; Formal wage employment, full-time; Formal wage employment, part time; Self-employed in agriculture; Self-employed making money, full-time; Self-employed making money, part-time; Other	Go to "Dem_Work_4"		
Dem_Work_3	What is the reason why you are not working? Please choose one from:	Waiting to continue agricultural work; Unemployed (looking for work);Unemployed (waiting to start new work);Unable to work (permanently sick or injured);Student; Housewife/homemaker (not looking for work); Other; not looking for work			

Dem_Work_4	Describe the work that you do or did in your most recent job. If you have more than one profession, choose the one you spend the most time doing. Please choose one from:	Farmer (own land);Farm work on employers land; Domestic ;Work in bar, hotel, guest house; Fishing; Mining; Working in shop; Informal Selling; Commercial sex work; Transport (trucker, taxi driver);Factory ; Guard (security company);Police/soldier; Clerical and office work; Government ; Teacher; health care ; Other Professional; Other			
Dem_Comm	How long have you lived in this community?	XX in years, months, weeks or days			Best guess/estimate
Dem_Abs_1	In the last 3 months, how many nights did you spend away from home?	# nights	If 0, go to Dem_Abs_5		RA training - "night spent" away = slept away
Dem_Abs_2	In the last 3 months, how many nights did you spend outside this community [community name]?	# nights	If 0, go to Dem_Abs_5		as above

Dem_Abs_3	What was the main reason you spent time outside this community - on the last occasion when you were away? Please choose from:	work or business; visiting family/leisure/holiday; other			only if ppt was away in last 3 months ie ≥1 for Q above; train RA to ask ppt to pick most appropriate (eg ppt may have work and visit family - pick main one based on greatest time spent).
Dem_Abs_4	How often do you usually spend time away from this community for the above reason? Please choose one from:	>once ever 3 months; once every 3 months; once every 6 months; once every year; once every >1year			once = one episode (not one night/day)
Dem_Abs_5	In the last year, how many nights did you spend outside this community [community name]?	# nights			Include last 3 months + other nights away in last year (at analysis, we can seperate out what was beyond 3months)
Dem_Abs_6	What was the main reason you spent time outside this community over the last year? Please choose from:	work or business; visiting family/leisure/holiday; other			
Dem_Abs_7	How often do you usually spend time away from this community for the above reason? Please choose from:	>once ever 3 months; once every 3 months; once every 6 months; once every year; once every >1year			
HH_1	Total Household Members	#			Including ppt
HH_2	Are you the Head of HH?	Yes; No	If yes go to Econ_Hous_1		

HH_3	How are you related to the Head of HH. Is he/she your ...? Please choose one from:	Husband; father; father-in-law; brother, brother-in-law; son, son-in-law; grandfather; uncle; nephew; Wife; mother; mother-in-law; sister; sister-in-law; daughter; daughter-in-law; grandmother; aunt; niece; cousin; friend; landlord; other			
Econ_Hous_1	Which of the following best describes the main type of building that this household occupies? Please choose one from:	single unit/brick structure on its own stand; cluster/multi-unit; traditional hut/structure made from traditional material; flat in block of flats; servant quarters; caravan/tent; hostel; shack; other			
Econ_Hous_2	What is the main type of flooring for this household? Please choose one from:	Dirt/earth; Wood/plank; Parquet; Lino; Cement; Tile; Other			
Econ_Hous_3	How many living and sleeping rooms are there in this housing unit?	XX rooms			

Econ_Hous_4	What is the main source of drinking water for this household? Please choose one from:	Piped indoors; Stand pipe/tap within plot; communal tap; borehole; Protected well; Unprotected/shallow well river/dam/lake/pan; bowser/tanker; other			
Econ_Hous_5	What is the main source of energy used for cooking? Please choose one from:	No cooking done in household; Electricity (mains);Electricity (individual solar); Gas; Paraffin; Charcoal; Wood; Other			
Econ_Hous_6	What is the main toilet facility used in your household? Please choose one from:	Own flush toilet; Shared flush toilet; own pit latrine; Shared pit latrine; Own VIP latrine; Shared VIP latrine; Pail/bucket; Communal chemical latrine; Bush; Other			
Econ_Ass	Does any member of your household have access to the following items in good working order? Please choose all that apply from:	Working Cellphone; bicycle; motorcycle or scooter; car/bakkie; Electricity to house; TV; Fridge/freezer; Radio; Computer/Laptop; CD or MP3 player; stereo/cassette /other music player;			Select all that apply

Econ_Inc_2	Do you or anyone in your household receive any government grants?	Yes; No			
Econ_Contr	Do you make decisions about how money is spent in your household? Please choose one from:	Yes (someone else's approval needed); Yes (no one else's approval needed); No		There is evidence that suggests women who have some financial autonomy, are more likely to take-up and follow-up with PMCT care, so we are interested in exploring similar for treatment uptake	
CHiP_exp_0	I would now like to ask you some Qs about your experience with the CHiP who came to your house to offer you services related to PopART. The information you give us will help the PopART team learn what they are doing well and what could be done better. Your answers in this study are completely confidential, will not be shared with CHiPs and the answers you give do not affect any of the services available to you (including the services provided by the CHiPs). No one will know what particular answers you give (including the CHiPs). Do you have any questions before we begin?				Note, in trainings it will be highlighted that it is important that RA is seen as separate from CHiPs. One is research the other intervention

CHiP_exp_1	This question is regarding the CHiP(s) who came to see you. Did you previously know the individual(s) BEFORE you first met them as a CHiP?	Yes; No			(If more than 1 CHiP - any of them); rely on ppts own definition of "know" someone
CHiP_exp_2	Did you know which community they come from when you first met them as a CHiP?	Yes; No	If yes, continue; if no go to CHiP_exp_4		
CHiP_exp_3	Do they come from this community (XX community name)?				
CHiP_exp_4	Please choose one from the following about whether you think confidentiality will be maintained after your encounter(s) with the ChiP?	Strongly agree; Agree; Disagree; Strongly Disagree			Training point - confidentiality still maintained if result discussed with ppt's permission/ for pt management. But breach of confidentiality if any client details discussed with other community members etc.
CHiP_exp_5	Please choose one from the following about whether you think that in general, the CHiP treated you with respect?	Strongly agree; Agree; Disagree; Strongly Disagree			
CHiP_exp_6	Please choose one from the following about whether you think that in general, the CHiP was someone you could talk to and answer questions openly?	Strongly agree; Agree; Disagree; Strongly Disagree			

ART_peer_0	For the next 2 Qs, please think about the first time when the CHiP referred you for HIV care at the clinic.			Note the CC study will be done upto 9m after the first encounter. We are trying to get at how the ppt felt at the time of deciding whether to take up testing. From CHiP EDC we will know time-line of when offer was first made and if multiple offers were made before test was accepted among controls. Recall bias is a valid concern but we will try our best!	Train RAs to ensure these next Qs are related to first referral by CHiP ie not follow-up /repeated visits. Responses from ppt to be based on their impressions (best guess) about their peers.
ART_peer_1	At that first time, did you already know people who had been on ART?	Yes; No	If no go to HIV_stat_0		
ART_peer_2	Who was it you knew, who had been on ART? Please choose <u>all</u> that apply from:	Sexual partner; Household member(s) (not including sexual partner); friend(s)/neighbour(s)/colleague(s); other			RA training to avoid double-counting (sexual partner and HH member)
HIV_stat_0	I would now like to ask you some questions about your HIV status. Can I proceed?				

HIV_stat_1	When was your first positive HIV test result? Please give the month and year. If you can't recall exactly, please give a best guess.	MM:YYYY			Note, these ppts should all be known HIV+ve in this study. Note, in Agree_1 already acknowledged that been referred for HIV services
HIV_stat_2	Have you disclosed your HIV status to anyone, except to me for the purpose of this study?	Yes; No	If no or no answer go to Sex_0		
HIV_stat_3	To whom did you disclose your HIV status?	husband/wife /Sexual partner; Family Member; Friend/neighbour/colleague; Religious leader/; Health care ; Other			
Sex_0	Now I would like to ask you some questions about your recent sexual activity. I know these questions are sensitive and want to remind you that your answers are completely confidential. Scientists are interested to know about patterns of sexual behaviours in the community and this information will not be linked to you as an individual. If anyone comes near us I will change the topic of conversation. If we should come to any questions that you don't want to answer, just let me know and we can decide if we should skip the question. Do you				

	have any questions before we continue?				
Sex_1	Have you ever had sex (meaning penetrative intercourse)?	Yes; No			
Sex_2	How old were you when you had sex for the first time? If you can't recall the exact age, please give a best guess.	XX years			
Sex_3	In your lifetime how many different people have you had sex with (including your husband/wife)? If you can't recall the exact number, please give a best guess.	XXX sexual partners			
Sex_4	Have you had sex in the past 12 months?	Yes; No	If No go to Stigma_0		
Sex_00	At this point, let me say that I understand that some of the Qs I ask you may seem inappropriate for your situation. Please know that I am asking them as part of standard list of questions which I have to ask everyone and I appreciate your patience and honesty when answering them,				

	remembering that your answers will be kept confidential.				
Sex_5	In the past 12 months, how many different people have you had sex with (including your husband/wife)? If you can't recall the exact number, please give a best guess.	XXX people	If 1 partner go to Part_one_0; 2 partners go to Part_two_0; ≥ 3 go to Part_three_0 (if 0 partners this Q would be skipped see - Sex_4 skip pattern)		
Sex_6	..., do any live outside of [community name]?	Yes; No; Don't now			
Part_one_0	I would like to ask more questions about the partner with whom you have had sex <u>most recently.</u> In order to ask the questions we will call this partner - Partner 1. Can I proceed?		Go to Part_one_1		
Part_two_0	I would like to ask more questions about the 2 partners with whom you have had sex <u>most recently.</u> In order to ask the questions we will list these 2 partners by number and then I will ask the same set of questions about each partner in turn. We will start with the partner you have had sex with		Go to Part_one_1 (which will be followed by same loop questions for Part_two)		

	most recently - who we will refer to as Partner 1. Can I proceed?				
Part_three_0	I would like to ask more questions about the 3 partners with whom you have had sex most recently. In order to ask the questions we will list these 3 partners by number and then I will ask the same set of questions about each partner in turn. We will start with the partner you have had sex with most recently - who we will refer to as Partner 1. Can I proceed?		Go to Part_one_1 (which will be followed by same loop questions for Part_two; then Part_three)		
Part_one_1	What was your relationship with "this partner 1" the last time you had sex? Please choose one from:	Husband/wife (i.e. married or living as married); Boyfriend/ Girlfriend; Casual partner known to you before having sex; One-time partner who was unknown to you before having sex; Other			
Part_one_2	Where was "this partner 1" living the last time you had sex?	Same house; Same community [insert name of this community]; Outside [insert name of this community]; Don't Know			

Part_one_3	How old is "this partner 1" ? If you don't know for sure, please give a best guess.	XX years			
Part_one_4	When did you first have sex with "this partner 1"? (Best guess)	MM/YYYY			
Part_one_5	How long ago did you last have sex with "this partner 1" ? If you are not sure, please give a best guess.	xxx days; Use calendar and help work out number of days.			
Part_one_6	The last time you had sex with "this partner 1" , did you/your partner use a condom?	Yes; No; Don't remember	If Yes, continue; If Don't remember or No answer go to Part_one_11		Can be male or female condom
Part_one_7	Did you drink alcohol before the last time you had sex with "this partner 1" ?	Yes; No; Don't remember			
Part_one_8	The last time you had sex with "this partner 1" , did you give or were you given money or a gift in order to have sex? It could be money (eg rent or fees for something), food, soap, transport, or clothing.	Yes, I Received money/gift; Yes, I gave money/gift; No, I did not give or receive money/gift	If yes, skip to Part_one_14 OR if Part_one_1 response is husband/wife, skip to Part_one_14		
Part_one_9	What is the HIV status of "this partner 1" ?	Positive; Negative; Don't know	If Negative or Don't know, go to Part1_16		
Part_one_10	Do you know if "this partner 1" is taking ART?	Yes, he/she is taking; No, he/she is not taking; Don't know			

Part_one_11	Over the past 12 months, during your relationship with "this partner 1" , do you know or suspect that this partner was having sex with someone else?	Yes – I know with another spouse; Yes – I know with another partner or partners; Yes - I believe there was another partner or partners; No, I know this partner did not have other partners; Don't know			
			If Sex_5=2 or Sex_5=3, proceed with partner loop Qs for each partner (max 3)		Programme loop Q+F102s to repeat according to answer in Sex_5
HIV self_risk_1	If you consider your behaviour (current or past) with respect to getting HIV (including anything entirely due to a sexual partner you are/were with) - would you consider that you have been at high risk of HIV?	Very high; somewhat high; somewhat low; very low			Training - to ensure prompting that if partner perceived to be high risk, this will be a "yes" for the ppt too (even if eg ppt is monogamous)
Stigma_0	Different people feel differently about people living with HIV. I am going to ask you about issues relevant to HIV and people living with HIV. Some of these questions will ask for your opinion on how you think people with HIV are treated. Using your own opinions and thinking about this community [community name], please tell me how strongly you agree or disagree to the following statements. Do you have any questions before we begin?				

Stigma_1	People think that having HIV is shameful and they don't want to be associated with me	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_2	People sometimes talk badly about people living with or thought to be living with HIV to others.	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_3	People living with or thought to be living with HIV are verbally insulted, harassed and/or threatened	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_4	I have felt ashamed because of my HIV status	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_5	I blame myself for getting HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_6	I think less of myself because of my HIV status	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_7	People sometimes talk badly about me because I am living with HIV.	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_8	I have been excluded from social gatherings or activities because I have HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_9	People have disclosed my HIV status to others wihtout my permission	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_10	People may think that I have been immoral/irresponsible as the reason behind why I have HIV	Strongly agree; Agree; Disagree; Strongly Disagree			
Stigma_11	I confronted, challenged, or educated someone who was stigmatising and/or discriminating against me	Strongly agree; Agree; Disagree; Strongly Disagree			

Stigma_12	A health worker may disclose to others without my permission that I am on treatment for HIV (if I am on treatment)	Strongly agree; Agree; Disagree; Strongly Disagree			
Health_0	I will now ask you questions about whether you have been unwell in the last 12 months. Do you have any questions before we begin?				
Health_1	During the past 12 months have you been unwell to the extent that you needed to seek advice about it?	Yes; No			
Health_2	If yes, approximately how many times in the last 12 months?	# (if not sure, best guess)			
Health_3	During the past 12 months which of the following did you go to for health care/treatment - please choose all that apply from:	Traditional/faith healer; Health worker at a health facility; Pharmacy or other drug vendor; other			All that apply
Health_4	In general, which of these would you consult first for a health related problem (if anyone)? Please choose one from:	Traditional/faith healer; Health worker at a health facility; Pharmacy or other drug vendor			Only one
Health_5	During the past 12 months, have you had to stay overnight in hospital for any illnesses?	Yes; No	If no, go to Health_8		
Health_6	During the past 12 months, how many times have you been hospitalised?	# times			
Health_7	During the past 12 months, what was the total duration of hospitalisation?	# days			

Health_8	During the past 12 months, have you paid for private health care?	Yes; No			Private health - may include HIV testing/ treatment/admission.
Circum_0	Now I would like to ask you about male circumcision. As a reminder, by male circumcision, I mean removal of the foreskin of the penis. I understand these Qs can be sensitive. The reason that I am about to ask them is so scientists can understand circumcision practices in this community, because medical male circumcision has been shown to be associated with HIV transmission. I would be grateful if you could answer as honestly as possible remembering that your answers are confidential. Before we begin, do you have any questions?		Only if Dem_Gen:Male		
Circum_1	Are you circumcised?	Yes; No; not sure;	If No, Not sure, go to SRQ_0		
Circum_2	At what age were you circumcised?	< 5years of age;XX years			
Circum_3	When were you circumcised?	MM/YYYY			If VMMC done - use circumcision "certificate" or other proof if available; if not - ppt self-report

Circum_4	What was the main reason why you were circumcised?	Tradition or religious; To protect myself against HIV; Hygiene; Other medical reason; Other; Don't know	If Don't know or No answer go to Circum_06		
Preg_0	I will now ask you questions about pregnancy and antenatal care. Do you have any questions before we begin?		Only if Dem_Gen:Female		
Preg_1	How many times have you given birth? Include both live births and stillbirths. Multiple births, such as twins, count as 1 birth.	# times	If #:0 go to SRQ_0		
Preg_2	When was the last birth?	MM/YYYY	If last birth < 12m ago continue, if >12m go to SRQ_0		
Preg_3	Did you go for antenatal care during this pregnancy?	Yes; No			
Preg_4	Were you tested for HIV during this pregnancy?	Yes; No; Don't know	If yes go to Preg_5; If no, go to Preg_6; If Don't know go to SRQ_0		
Preg_5	When was that?	MM:YYYY (if not sure, best guess)	Go to Preg_7		
Preg_6	Why were you not tested for HIV during this pregnancy?	Did not agree to testing; Not offered / did not attend a clinic where testing is available; Husband/partner refused; Already knew I was HIV positive; other	Go to SRQ_0		

Preg_7	Were you given ART for you to take to protect your baby?	Yes;No; Don't know; Not yet received; Already on ART before attending ANC			
SRQ_0	The following questions are related to certain pains and problems, that may have bothered you in the last 30days. If you think the question applies to you and you had the problem described in the last 30days, answer YES. On the other hand, if the question does not apply to you and you did not have the problem in the last 30days, answer NO. If you are unsure please give the best answer you can. To remind you again, all your reponses are confidential.				Yes =1 and score of 6 or greater = suggestive of mental disorder
SRQ_1	Do you often have headaches?	Yes; No			
SRQ_2	Is your apetite poor?	Yes; No			Poor apetite = low interest in food
SRQ_3	Do you sleep badly?	Yes; No			
SRQ_4	Do you cry more than usual?	Yes; No			
SRQ_5	Do you find it difficult to enjoy your daily activities?	Yes; No			
SRQ_6	Do you find it difficult to make decisions?	Yes; No			
SRQ_7	Is your daily work suffering?	Yes; No			
SRQ_8	Are you unable to play a useful part in life?	Yes; No			
SRQ_9	Has the thought of ending your life been on your mind?	Yes; No			
SRQ_10	Do you feel tired all the time?	Yes; No			- for reasons that cannot be explained

Alcohol_0	I will now ask you questions about drinking alcohol and drug use. I know these questions are sensitive and want to remind you that your answers are completely confidential. Do you have any questions before we begin?				
Alcohol_1	How often do you have a drink containing alcohol?	(0) Never ; (1) Monthly or less; (2) 2 to 4 times a month; (3) 2 to 3 times a week; (4) 4 or more times a week REVERSE ORDER OF OPTIONS	If zero go to Alc_9		Training - reassure ppts that Alc_9 and 10 are std and still asked of everyone even if score here is zero.
Alcohol_2	How many drinks containing alcohol do you have on a typical day when you are drinking?	(0) 1 or 2; (1) 3 or 4; (2) 5 or 6; (3) 7, 8, or 9; (4) 10 or more			
Alcohol_3	How often do you have six or more drinks on one occasion?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily	Skip to Alc_9 if Total Score for Questions 2 and 3 = 0		
Alcohol_4	How often during the last 12 months have you found that you were not able to stop drinking once you had started?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_5	How often during the last 12 months have you failed to do what was normally expected from you because of drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			

Alcohol_6	How often during the last 12 months have you needed a first drink in the morning to get yourself going after a heavy drinking session?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_7	How often during the last 12 months have you had a feeling of guilt or remorse after drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_8	How often during the last 12 months have you been unable to remember what happened the night before because you had been drinking?	(0) Never; (1) Less than monthly; (2) Monthly; (3) Weekly; (4) Daily or almost daily			
Alcohol_9	Have you or someone else been injured as a result of your drinking?	(0) No ; (2) Yes, but not in the last year; (4) Yes, during the last year			
Alcohol_10	Has a relative or friend or a doctor or another health been concerned about your drinking or suggested you cut down?	(0) No ; (2) Yes, but not in the last year; (4) Yes, during the last year			
Alcohol_11	Among people of similar age and sex as you in this community during an average month, how common do you think it is for them to have six or more drinks on one occasion?	Very common; somewhat common; somewhat uncommon; very uncommon			
Drugs_1	In your lifetime have you ever used any drugs recreationally?	Yes; No	If no or refused – If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		

Drugs_2	In the last 12 months, have you used drugs recreationally?	Yes; No	If no or refused – If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		
Drugs_3	In the last 12 months, which drugs have you used?	Cannabis/Marijuana; Cocaine/Crack; Khat/Miraa; Ecstasy/Disco biscuit; Heroin; Amphetamine/Speed;Tik; Nyamba (any drug mixed with ART and smoked); Glue/solvents/petrol sniffing;Other	If Dem_Gen:Female go to IPV_0; if Dem_Gen:Male go to IPV_7		
IPV_0	I would now like to ask you some questions about your relationship(s) and how any partner during the last 12 months treated you. If anyone comes near us I will change the topic of conversation. I would again like to assure you that your answers will be kept confidential. If we should come to any questions that you don't want to answer, just let me know and we can decide if we need to skip the question. Do you have any questions before I begin?			There could be different ways of addressing the issue of GBV - but on balance we have gone with any partner of last 12m and Qs related specifically to IPV ie not overall violence women may be subjected to in the community (so does not include rape by a stranger etc).I think this is the most pertinent to explore wrt asso with uptake of testing. Qs are	

				largely based on DHS questions.	
IPV_1	In the last 12 months, how often has a partner verbally insulted you or humiliated you in front of other people, or intimidated or threatened to hurt you?	Often; A few times; Once; Never	If no go to IPV_3		Training to emphasise this Q is about non-physical/sexual abuse rather verbal/ other intimidation.
IPV_2	When was the last time any of the above happened?	MM:YYYY		Approximate	
IPV_3	In the last 12 months, how often has a partner physically hurt you eg slapped, kicked, pushed, punched, beaten or otherwise physically hurt you?	Often; A few times; Once; Never	If no go to IPV_5		
IPV_4	When was the last time any of the above happened?	MM:YYYY		Approximate	
IPV_5	In the last 12 months, how often has a partner made you have	Often; A few times; Once; Never	If no go to IPV_7		

	sexual activities when you did not want to?				
IPV_6	When were you last made to have sexual activities when you did not want to?	MM:YYYY		Approximate	
IPV_7	In this community how common do you think it is for people to believe a husband is justified in physically hurting his wife if he has a reason	Very common; somewhat common; somewhat uncommon; very uncommon			
IPV_8	In this community how common do you think it is for people to believe a husband is justified in making his wife have sexual activities with him if he wants to	Very common; somewhat common; somewhat uncommon; very uncommon			
IPV_!!	If experience of IPV - I'm sorry to hear about what has happened to you. If you wish we can provide information on what help might be available for you, before I leave.				Programme prompt at end of survey to provide further information.
Percep_0	I am going to provide you with some statements about HIV testing and about the PopART trial and would like you to choose the most appropriate response. As before, your answers will not be shared with anyone outside of the study team (including the CHiPs) in a way that can be connected to you. The answers you give do not affect any of the services available to you in this community or elsewhere - whether as part of				

	PopART or otherwise. Can I proceed?				
Percep_1	The activities promoted by the PopART trial can increase the number of people having an HIV test in your community	Strongly agree; Agree; Disagree; Strongly Disagree		If ppts unclear about the activities - RAs can illustrate using study inforamtion sheets which ppts are routinely given by CHiPs in PopART intervention communities.	
Percep_2	The activities promoted by the PopART trial can increase the number of people having treatment for HIV in your community	Strongly agree; Agree; Disagree; Strongly Disagree			
Percep_3	Maximising the number of HIV infected individuals on treatment can help reduce the amount of new HIV infections arising in your community	Strongly agree; Agree; Disagree; Strongly Disagree			
Percep_4	Condoms are not required to prevent HIV transmission if infected individuals are on treatment	Strongly agree; Agree; Disagree; Strongly Disagree			

Percep_5	What do you think about the PopART trial being delivered in your community	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it	If Strongly agree or Agree, go to Percep_7		
Percep_6	Which of these is the most important explanation for why you disagree with the PopART trial being delivered in your community? Please choose all that apply from:	The CHiPs workers ask too many questions; the CHiPs workers pressure people to test for HIV or to talk to them; HIV testing/talking about HIV at home is not a good idea; doing research in my community is not a good idea; other			
Percep_7	What do you think about offering households members HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			
Percep_8	What do you think about offering couples HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			
Percep_9	What do you think about providing household members results of HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			

Percep_10	What do you think about providing household members results of HIV testing together at home?	Strongly agree with it; Agree with it; Disagree with it; Strongly Disagree with it			
HIV care_0	Now we have some questions about HIV testing and treatment. We will also talk about the first time that the CHiP advised you to attend the clinic (CHiP referral) and also about whether you enrolled for HIV care. As before, your answers will be kept completely confidential and will not be shared with anyone outside of the study team (including the CHiPs or clinic staff) in a way that can be connected to you. The answers you give do not affect any of the services available to you in this community or elsewhere - whether as part of PopART or otherwise.				
Test_1	Did you have a test with a PopART CHiP?	Yes; No		Note, clients may have tested before CHiPs and self-report +ve status to CHiPs	

Test_2	The last time you were tested for HIV, where were you tested? Please select one from:	Government hospital or clinic (includes ANC, TB, etc.); Private/church/mission hospital or clinic; Stand-alone HIV testing centre; Mobile testing site(caravan, tent, etc.; Work place; Home with CHiP; Home not with CHiP; Other place			
Test_3	When was the last time you were tested for HIV? If you don't know the exact date, give a best guess.	MM:YYYY			
Test_4	Have your disclosed the result of you last HIV test with anyone? (not including me)	Yes; No			
Reg_1	Have you ever registered for HIV related medical care?	Yes; No	If no go to PoCH-R_0	registered= enrolled=HIV care number/ID given	
Reg_2	Do you have your HIV care number?	Record number preferably from card; Card not available; Did not agree			
Reg_3	When did you first register for HIV care?	MM:YYYY Provide option to indicate if proof seen vs verbal report only			Use clinic card or other proof if available
Reg_4	Which clinic did you register at?	XX			
Reg_5	When you were referred by a CHiP had you already registered for HIV care at some point before that?	Yes; No	If no go to PoCH-R_0		RA training - emphasise before CHiP

PreCH-R_1	Thinking of that period of HIV care before being referred by a CHiP - had you discontinued / interrupted from care at any time?	Yes; No	Continue either response	Discontinued / interrupted = not attended for allocated appt.	
PreCH-R_2	At the time when you were referred by a CHiP - were you actively in HIV care?	Yes; No	If yes, go to PoCH-R_8; if no, continue	Actively in HIV care = attending for given appointments	
PoCH-R_0	Now thinking of the period <u>after</u> you were referred by a CHiP...		Use as stem for PoCH-R_0 Qs		
PoCH-R_1	Did you go to the clinic?	Yes; No	If no, go to PoCH-R_5; if yes, continue		
PoCH-R_2	Did you register for care after referral by a CHiP?	Yes; No	If yes, go to PoCH-R_5; if no, continue		
PoCH-R_3	Did you go but leave the clinic without registering?	Yes; No	If no go to PoCH-R_5		
PoCH-R_4	After going to the clinic what was the reason you left without being registered - please choose one from:	I was given another date to return by clinic staff; I was sent away by clinic staff without a date to return; I decided to leave; other		I decided to leave = of own accord	
	Different factors may influence someone's choice on whether to attend/register for HIV care. The following sets of questions are about the factors which may have encouraged or discouraged you from attending/registering. Consider these questions about pros and cons for you regardless of your final decision ie whether				RA training Q is about pros/cons around registeration for care after referral by CHiP

	you finally regsitered for care or not.				
PoCH-R_5	When referred by the PopART CHiP, did any of the following encourage you to attend/register for HIV care?				
PoCH-R_5_1	I had difficulty with the time it would take - because of my livelihood/job	Yes; No			
PoCH-R_5_2	I had difficulty with the time it would take - because of housework	Yes; No			
PoCH-R_5_3	I could not go to the clinic because it is too far away/time it would take to travel there	Yes; No			
PoCH-R_5_4	I could not go to the clinic because of transport costs to get there	Yes; No			
PoCH-R_5_5	I could not go to the clinic because it is only open during hours when I am at work	Yes; No			
PoCH-R_5_6	I think people get treated badly by clinic staff if they are HIV+ve	Yes; No			
PoCH-R_5_7	The clinic is too crowded	Yes; No			
PoCH-R_5_8	People have to wait for a long time in the clinic	Yes; No			
PoCH-R_5_9	The clinic is a place for those who are weak/women/children, and not for me	Yes; No			

PoCH-R_5_10	I am not ready to go to the clinic for HIV care	Yes; No			
PoCH-R_5_11	I will only go if/when I feel sick	Yes; No			
	Thinking about registration for HIV care after you were referred by CHiPs...		use as stem for PoCH-R_6-8		
PoCH-R_6	When did you register for HIV care?	MM:YYYY **Provide option to indicate if proof seen vs verbal report**			Use clinic card or other proof if available
PoCH-R_7	Which clinic did you register at?	free text			
PoCH-R_8	Have you discontinued / interrupted from care since registering for care?	Yes; No			
Care_1	Are you currently in HIV care?	Yes; No			
Care_2	When did you last attend the clinic for HIV care?	MM:YYYY			
Care_3	For this most recent outpatient medical care visit, how long did it take you to get to the clinic?				
Care_4	How long did you spend in the clinic in total at your last visit?	< 1 hour, ≥1-2h; ≥2-3h; ≥3-4h; ≥4h			
Care_5	Have you had a CD4 count blood test?	Yes; No; Don't know	If no or don't know, go to Care_7		RA to provide std explanantion of CD4 count if ppt not familiar.
Care_6	What was the result of you last CD4 count? If can't remember exactly, please give your best guess.	XXX; Don't know **Provide option to indicate if proof seen vs verbal report**			Use clinic card or other proof if available
Care_7	At your last visit, was the time you had to spend in the clinic acceptable? Please choose one from the followin:g	Strongly agree; Agree; Disagree; Strongly Disagree			

Care_8	In general, did the clinic staff treated with you respect? Please choose one from the following	Strongly agree; Agree; Disagree; Strongly Disagree			
Care_9	In general, were you worried about someone you know seeing you in the clinic?	Yes; No			
EvART_1	Has a health care worker recommended that you start antiretroviral therapy or ART ?	Yes; No; Don't know			
EvART_2	Have you ever taken any ART?	Yes; No; Don't know	If no go to FavART_2_0		
EvART_3	When did you first start taking ART?	MM:YYYY (verify with ART card) **Provide option to indicate if proof seen vs verbal report**			
EvART_4	Did you first start taking ART before or after referral by a CHiP?	Before; after	If after, go to PoCH-ART		RA training - emphasis on FIRST ART
PreCH-ART_0	Thinking about any ART taken before you were referred by a CHiP...		Use as stem for each PreCH-ART Q		
PreCH-ART_1	Did you ever stop taking ART?	Yes; No	If no, go to Ineligible after confirming ART started before CHiPS and never stopped ie was already on ART (and on it) when saw CHiP ie ineligible for CC2		

PreCH-ART_2	Why did you stop taking ART?	Doctor told me I didn't need them; Traditional Healer / Religious Leader told me I didn't need them; Husband/Wife asked me to stop; I ran out of pills/ didn't fill prescription; Out of stock at the clinic/pharmacy; I feel well/ I don't think I need them/ I am cured ;Too many pills; They don't work; They make me sick; Too difficult/expensive to get to facility to collect them; I was only taking them during pregnancy/ to protect my baby (PMTCT intermittent);I felt ashamed to take them/I didn't want anyone to know; Other;			
PreCH-ART_3	Were you taking ART at the time when you were first seen by a CHiPs?	Yes; No	If yes, go to FavART_2		
PoCH-ART_0	Now thinking of the period <u>after</u> you were seen by by a CHiP...		Use as stem for Qs on PoCH-ART, FavART and AgART		

PoCH-ART_1	Did you first start or re-start ART after referral by a CHiP?	Yes; No	If no go to FavART_2_0		First start or re-start depending on responses to above
PoCH-ART_2	When did you start/re-start taking ART?	MM:YYYY (verify with ART card) Provide option to indicate if proof seen vs verbal report only			
PoCH-ART_3	Did you start/re-start ART within 3 months of being referred by a CHiP?	Yes; No			
FavART_1	In your own words what was you main reason for starting/re-starting ART after being referred by a CHiP?				RA to select most suitable from drop-down menu - same list as FavART
	Different factors may influence someone's choice on whether to start treatment. The following sets of questions are about the factors which may have encouraged or discouraged you from starting. Consider these questions about pros and cons for you regardless of your final decision ie whether you finally started ART or not.				
FavART_2_0	Did any of the following encourage you to start ART?				
FavART_2_1	For my own health even though I did not feel unwell before starting	Yes; No			
FavART_2_2	For my own health because I was feeling unwell before starting	Yes; No			
FavART_2_3	To protect my partner from getting HIV from me	Yes; No			

FavART_2_4	Recommended by health are worker (including CHiPs)/ clinic staff	Yes; No			
FavART_2_5	To protect my baby from getting HIV infection while I was pregnant/breast-feeding	Yes; No	(women only)		
FavART_2_6	I know someone/others who are well on ART and want to be on it too	Yes; No			
AgART_1	In your own words what was you main reason for not starting ART?				RA to select most suitable from drop-down menu - same list as AgART
AgART_2_0	Did any of the following discourage you from starting ART?	Yes; No		Note, there is deliberately some overlap with reasons for not going to clinic - but they're not the same Qs	
AgART_2_1	I could not or did not want to go to the clinic	Yes; No			
AgART_2_2	Going to the clinic for treatment is too time-consuming	Yes; No			
AgART_2_3	I was worried someone would find out about my HIV because of taking treatment/going to the clinic	Yes; No			
AgART_2_4	Who was it that you did not want finding out about your HIV because of taking treatment/going to the clinic? Please choose all that apply:	Sexual partner; Household member(s) (not including sexual partner); friend(s)/neighbour(s)/colleague(s); other			

AgART_2_5	I was/am not ready to take treatment	Yes; No			
AgART_2_6	I didn't think the treatment works so there was no point in starting it	Yes; No			
AgART_2_7	I think people get worse (or die) because of the treatment	Yes; No			
AgART_2_8	I didn't like the idea of taking life-long treatment	Yes; No			
AgART_2_9	I think I would have to make too many life-style changesto take ART (eg how I eat/ how much alcohol I drink / how much I go out socially etc)	Yes; No			
CuART_1	Are you currently taking ART?	Yes; No	If no or no answer, go to CuART_3	Current = ART taken in the last 7d	
CuART_2	In the past 7 days, did you miss taking any of your ART pills?	Yes; No			
CuART_3	Have you ever hidden your ART pills so that others couldn't see them?	Yes; No			
CuART_4	In the past 12 months, have you ever stopped taking ART?	Yes; No	If No or No answer, go to Concl_0		
CuART_5	When did you stop taking antiretroviral therapy? If you have stopped taking ART on more than one occasion, please tell me the most recent time you stopped taking ART.	MM:YYYY; If month not known just enter year.			

CuART_6	Why did you stop taking ART (at the most recent time you stopped)?	Doctor told me I didn't need them; Traditional Healer / Religious Leader told me I didn't need them; Husband/Wife asked me to stop; I ran out of pills/ didn't fill prescription; Out of stock at the clinic/pharmacy; I feel well/ I don't think I need them/ I am cured ;Too many pills; They don't work; They make me sick; Too difficult/expensive to get to facility to collect them; I was only taking them during pregnancy/ to protect my baby (PMTCT intermittent);I felt ashamed to take them/I didn't want anyone to know; Other;			
Concl_0	Thank you very much for your cooperation. The information you provided is very helpful and we appreciate your time and assistance. Do you have any final questions or comments that you would like to share with me?		Go to End_01		

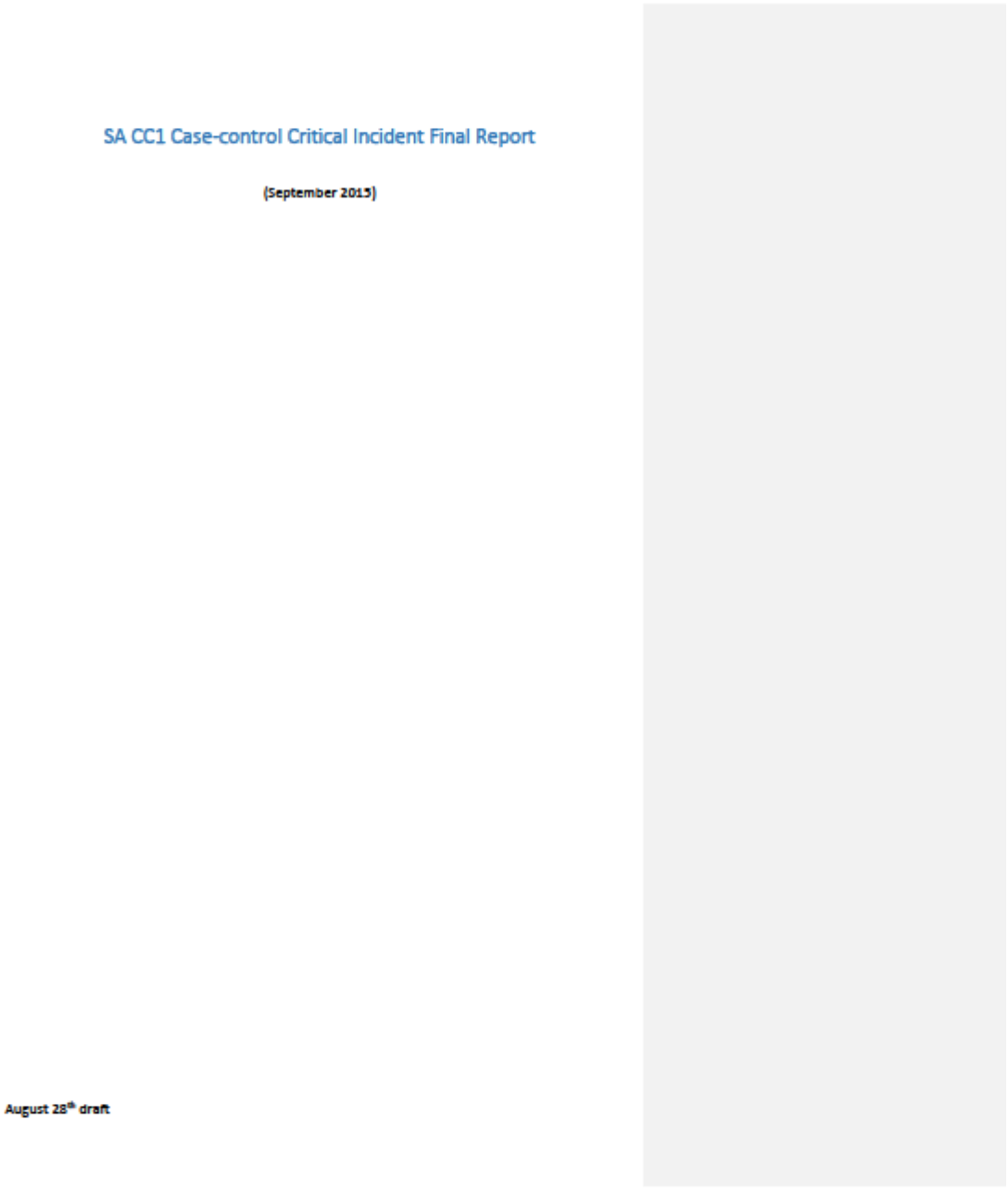
Further research participation permission	If you are interested, we would like to enter your name on a list from which you may be selected to participate in further research. Would you be interested in being included in such a list? If so, we will enter your name, address, date of birth and gender on a list and a researcher will come to explain the next study to you. Once you fully understand what the study involves you will be asked for your written consent to participate in the study. At that time, you can decline to participate in the study if you decide not to proceed for any reason. If you decline at any stage, you will still receive all the services that are available to other community members here. Would you be interested in being included in such a list?	Yes;No			
IPV	For participants with experience of IPV - provide contact information of police and NGOs working on IPV support				

Appendix 8: Link to South Africa Case-control Study 1 Critical Incident Report 1

SA Case-Control Study 1 Critical Incident report

August 2015

Appendix 9: Link to South Africa Case-control Study 1 Critical Incident Report 2



Appendix 10: Link to US Department of Health and Human Sciences and HIV Prevention Trials Network Office of Research Integrity Final Report

To: HHS, ORI, DIO
Inquiry Report
Re: DIO 6015
From: FHI 360 (Deborah Kennedy, COO)
Prepared for Submission on November 6, 2015

Abbreviations / Acronyms

CC1	Case Control Study 1 (a nested study within HPTN 071, or PopART)
CHiPs	Community HIV Care Providers
DAIDS	Division of AIDS (a division of NIAID)
DIO	Division of Investigative Oversight (within HHS ORI)
DSMB	Data Safety and Monitoring Board
DTTC	Desmond Tutu TB Centre
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HBHCT	Home-based HIV Counseling and Testing
HHS	US Department of Health and Human Services
HPTN	HIV Prevention Trials Network
HPTN 071	Population Effects of Antiretroviral Therapy to Reduce HIV Transmission Study (PopART)
HR	Human Resources
HREC	Health Research Ethics Committee
LSHTM	London School of Hygiene and Tropical Medicine
NIAID	National Institute of Allergy and Infectious Diseases (an institute at NIH)
NIH	National Institutes of Health (an agency of HHS)
ORI (HHS)	Office of Research Integrity, US Department of Health and Human Services
ORI (SU)	Office of Research Integrity, Stellenbosch University
PHS	Protection of Human Subjects
PLS	Participant Log Sheet
RA	Research Assistant
RIO	Research Integrity Officer
SU	Stellenbosch University

Table 1: Key Individuals and Affiliations

RIOs	
Deborah Kennedy, MA Chief Operating Officer FHI 360 *FHI 360 Research Integrity Officer* (D Kennedy)	Malcolm de Roubaix, MPhil, DPhil, MD Faculty Center for Medical Ethics and Law Stellenbosch University *SU Alternate Research Integrity Officer* (M de Roubaix)
FHI 360 Inquiry Committee	
Carol Dukes Hamilton, MD, MHS Director, Scientific Affairs FHI 360 *Committee Chair* (C Hamilton)	Amy Corneli, PhD, MPH Instructor, Department of Medicine Duke University *Committee Member* (A Corneli)
John Stanback, PhD, MA	Stacey Succop, MPH, PMP

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Appendix 11: South Africa Case-control Study 1 Data Verification Questionnaire

Factors associated with the uptake and non-uptake of Home-Based Voluntary HIV testing and Counseling during the first annual round of the PopART interventions (Case-Control study 1)

We are conducting a review of processes during one of our studies – the Case Control Study (1). During the study, the Research Assistants asked selected community members a number of questions to try to identify differences between people who accepted HIV testing offered by the PopART CHiPs, and those who chose not to accept testing.

We appreciate you taking time to talk to us and very much value your contribution. We are making a follow-up visit to participants who were selected for the study to monitor the quality of the information which has been collected. We do this in order to ensure that we conduct high quality research and that only accurate information is included in the study. I/we would therefore like to ask you a few questions and this will take no more than 15 minutes of your time. Do you have any questions before I/we begin?

Q1	What is your name?	Free text	
Q2	Did you participate in the Case-control study (1)?	Yes; No; Not sure	
Q3	Is this your signature? (show copy of consent form we have on record at DTTC)	Yes; No	
Q4	What is your age (in years)?	_ _ y	
Q5	What is the highest grade of education that you have completed? Please choose one from:	None; Grade 1; Grade 2; Grade 3; Grade 4; Grade 5; Grade 6; Grade 7; Grade 8; Grade 9; Grade 10; Grade 11; Grade 12; College/University; other	

Q6	When did you complete the above level of education?	Month; Year	
Q7	What is your religion? Please choose one from:	Christian; Islam; Baha'i faith; Buddhism; Hinduism; Judaism; Animist; Traditionalist; No religion ; Other	
Q8	How long have you lived in this community?	XX in years, months, weeks or days	
	Now I would like to ask you about male circumcision. As a reminder, by male circumcision, I mean removal of the foreskin of the penis. I understand that the question is sensitive. I would be grateful if you could answer as honestly as possible - your answers are confidential. Do you have any questions?		Only if Male
Q9Ma	Are you circumcised?	Yes: No; Not sure;	Only if male
Q10M	When were you circumcised?	Month; Year	
	I will now ask you questions about pregnancy and antenatal care.		Only if Female
Q9F	How many times have you given birth? Include both live births and stillbirths. Multiple births, such as twins, count as 1 birth.	# times	
Q10F	When did you last give birth?	Month; Year	

Thank you for answering our questions. We have 3 more questions we would like to ask you with regard to your experience with participating in a study, and we would also like to ask about any additional feedback you have for us.

Q11	How did you experience the case-control study and procedure?	Free text	
Q12	How does it feel to be a research participant?	Free text	
Q13	How were you treated as a research participant by the research team?	Free text	
Q14	Do you have any additional comments?	Free text	

We would like to thank you again for helping us collect this valuable information. Is there anything you would like to tell me/us or ask me before I/we leave?

Data collected by –

Name:

Signature:

Date:

i By 12m FU, LTFU reported among all individuals, including individuals on ART. Denominator therefore includes N=254 known HIV+ & on ART

ii Not reported (NR) as outcome not reported separately for those detected through HB-HTS

iii Loss to follow-up is reported as individuals not followed-up at 9m; some of these individuals contributed to analysis of LTC and/or ART prior to being LTFU

iv Not applicable (NA): Individuals defined as “not linked to care” regardless of whether or not the individual was contactable. Among individuals not LTC, reasons available for N=442: Asked not to be called (14%; n=63); Deceased (0.2%; n=1); Called many times (56%; n=249) Incorrect information (18%; n=79); No telephone (11%; n=50)